

Effectiveness of case management on clinical outcomes in women with cervical cancer: A systematic review with meta-analysis

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Abstract: Background: Cervical cancer is the fourth common type of cancer and can be deteriorated by insufficient care management. Case management, a collaborative process utilizing available resources to satisfy individual health needs and attain cost-effective outcomes, has been applied in management of cervical cancer. Aims: To evaluate the effectiveness of case management on clinical outcomes in patients with cervical cancer compared with non-case management care. Methods: The following databases were searched: Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science. Grey literature searches were performed as well until September 2017. For continuous outcomes, the mean difference or standardised mean difference along with 95% confidence interval were extracted; for dichotomous data, the corresponding odds ratio with 95% CI was calculated. A fixed- or random-effect model is applied for meta-analysis when appropriate. Heterogeneity was assessed by the I^2 statistics. Results: Ten studies were included in this review, comprising four randomised controlled trials and six non-randomised studies and involving 5980 participants with low to moderate overall risk of bias. Case management interventions varied in the models and contents. During diagnosis identification phase, the case management groups were improved significantly in adherence to follow-up in six months and over twelve months; in timely diagnosis resolution in two months, twelve months and eighteen months; and in time to initiation of colposcopy follow-up and time to diagnosis resolution. During treatment period, case management was found more effective at the following items: the rate of patients continuing treatment in the same institute; the rate of planned readmission for active treatment in fourteen days; the rate of planned readmission for active treatment in 15-30 days. There were no statistical differences in treatment phase between groups in the rate of prolonged hospitalisation, the rate of nonadherence to treatment, and the rate of unplanned hospital readmission. Several studies concluded that age, insurance status, literacy ability, and severity of screening abnormality may affect follow-up behaviour. Conclusion: Relatively robust evidence is provided by several high-quality studies that case management improves clinical outcomes in cervical cancer at specified time points. Age, insurance status, literacy ability, and severity of abnormality affect the adherence to follow-up and treatment. Whereas in view of heterogeneity in the components of intervention and outcome measures across the included trials, more rigorously-designed studies are needed in the future to explore further cost-effective protocols of case managements maximising adherence to follow-up and treatment, and relevant barriers should be investigated further as well.

Keywords: cervical cancer; case management; systematic review; meta-analysis

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doi: 10.18686/jn.v7i1.140

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1. Introduction

Cervical cancer is the fourth common type of cancer and about half a million new cases occur annually worldwide (Denny, 2015; Ebisch *et al.*, 2016). The impact of cervical cancer can give burden to patients and society due to inability to work, long periods of sick leave, decreased abilities of self-administration in daily life, and poor health (Yabroff *et al.*, 2011). Cervical cancer is also one kind of highly preventable disease, and curable if detected in the early stage, or else it will have high rate of morbidity and mortality without sufficient care management.

Diagnostic delay and sequential delayed treatment affect negatively on cancer outcomes, resulting in high mortality in low socioeconomic women in USA. In view of individual-level barriers impeding the initiation of timely follow-up and treatment, a national guideline was enacted by Centre of Disease Control (CDC) to guide the implementation of case management in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) (Vourlekis *et al.*, 2005). The focus of case management in Taiwan is to remove obstacles in illness trajectory and to facilitate therapy other than to eliminate barriers due to cultural and racial disparities (Yan *et al.*, 2009). The clinical outcomes were improved by case management in terms of timely diagnosis, timely initiation of cancer treatment, decision-making, and adherence to cancer. The other indicators were also salient including resource support, availability of medical staff, financial assistance, and waiting time in hospital (Lin *et al.*, 2016).

Optimal multidisciplinary treatment plans play a key role in improving adherence to screening and follow-up (Al-Mansour *et al.*, 2010). Case management interventions cater for the complex demands through supplying high-quality care at the price of low cost (Bachmann-Mettler *et al.*, 2011). Case management was shown to be effective in helping women to accept cancer screenings, receiving timely diagnostic resolution after cancer screening abnormality, initiating timely and proper treatment, and improve quality of life after cancer diagnosis (Krok-Schoen *et al.*, 2016). The effectiveness of case management is embodied by lower readmission to hospital, fewer cancer-related complications, and faster recovery. By linking women to social resources, communicating with clinicians, and navigating clinical environments, case management is usually applied to address potential barriers both in social and medical facets and identify health determinants (Meisinger *et al.*, 2013).

While case management is usually used to ensure follow-up rate of patients with abnormal screening results, there is still no definite conclusion about the effectiveness of case management on the prevention and treatment of cancer (Bachmann-Mettler *et al.*, 2011). A systematic review consisting of seven trials concluded that no effective evidence about positive influence of case management arising from diversity of interventions and trial endpoints (Wulff *et al.*, 2008). In addition, research studies reported the impact of case management on patients with various types of cancer, and the proportion of patients with cervical cancer is small (Aubin *et al.*, 2012; Krok-Schoen *et al.*, 2016). Therefore, there is a need to conduct a systematic review specialising in evaluating the effectiveness of case management on the prevention and treatment of cervical cancer.

2. Aims

This review aimed to analyse the contents of case management approaches studied in the literature to explore key variables affecting intervention outcomes (e.g. organisational and structural components of case management, methodology of studies), and to evaluate the effectiveness of case management to clinical outcomes of people with cervical cancer.

3. Methods

3.1 Search methods

The following databases were searched: Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science. Grey literature searches were performed as well. The searching periods ranged from database start date to September 2017. Searching terms included case management, care manager, patient care management, intensive case management,

patient care team, managed care programs, managed care, patient navigation, cervical cancer, cervical carcinoma, uterine cervix neoplasms, and cervical intraepithelial neoplasia.

3.2 Types of studies

Studies included randomised controlled trials and non-randomised studies focusing on case management interventions in the secondary and tertiary prevention of cervical cancer. The following types of studies were included and reviewed: randomised controlled trials (RCTs); controlled clinical trials (CCT) where participants were assigned prospectively to different arms through non-randomised allocation methods, e.g. patient identifier, date of birth, and alternation; controlled before and after study (CBA). There were no limitations in publication languages.

3.3 Types of participants

Women were included at the age of 18 years or older, with abnormal screening results or diagnosed with cervical cancer of any histological subtype, no matter which kind of therapy methods they received. Screening abnormality means: 1) visible or suspicious lesion on cervix; 2) either low- or high-grade abnormality. Screening abnormality includes: atypical squamous intraepithelial dysplasia (ASID), high-grade squamous intraepithelial lesion (HGSIL), and low-grade squamous intraepithelial lesion (LGSIL)). Histological subtypes of cervical cancer include: adenocarcinoma, squamous cell carcinoma, adeno-squamous carcinoma, and other cancer types according to International Federation of Gynecology and Obstetrics (FIGO) stage (FIGO 2014). The included studies were limited to focus on patients during diagnosis identification and treatment periods other than screening period.

3.4 Types of interventions

Well-defined interventions were included with the definite purpose of exploring the impact of case management on clinical outcomes in cervical cancer. Included studies compared case management with routine care in equivalent circumstances. However, most interventions answering effect of case management are not necessarily described as “case management”, therefore the interventions with similar components were searched such as shared care, care management, telephone follow-up, and patient navigation. Intervention contents include care organisation, multidisciplinary co-ordination, and interpersonal communications between the case manager and patient with the aim of educating, advocating and supporting patients.

3.5 Types of control group

The control group received care as standard care, routine care, enhanced standard care, or other non-case management in equivalent settings. This was comprised of isolate or collaborative care in diverse hierarchies, for instance, primary health care, secondary health care, and tertiary care.

3.6 Types of outcome measures

To acquire as much information of case management as possible, multiple measures were used. The outcomes included objective measures from medical records, and subjective materials from self-reported scales with known reliability and validity. For the purpose of the analysis, outcomes were grouped according to time points, such as six months, twelve months, over twelve months, and eighteen months.

3.7 Data analysis

The researchers contacted the article authors if the mean or standard deviation (SD) of key study outcomes were missing. For continuous outcomes, the mean difference or standardised mean difference along with 95% confidence interval (CI) were extracted; for dichotomous data, the corresponding odds ratio with 95% CI was calculated. A fixed- or random-effect model is applied for meta-analysis when appropriate. Heterogeneity was assessed by the I^2 statistic.

4. Results

There is a total of 10 studies included in this review. It comprised of four RCTs and six non-randomised studies. The study searching diagram was shown in **Figure 1**.

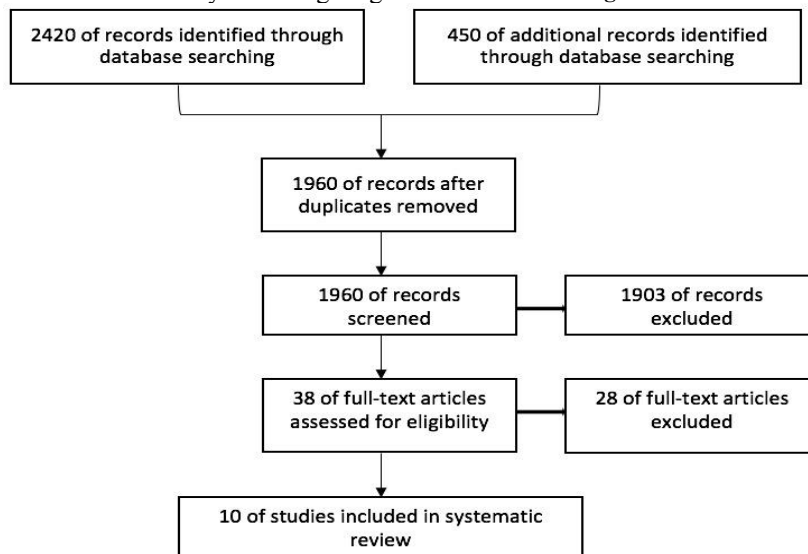


Figure 1. Study searching diagram.

4.1 Risk of bias in included studies

The tool recommended by Cochrane Collaboration was used to assess the risk of bias across the ten studies (Higgins, Green, 2011). The biases found most frequently consisted of random sequence generation, allocation concealment, incomplete data, and contamination between intervention and control groups (**Figure 2**). It was particularly notable that in majority of studies, blinding of personnel and participants was not reported.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Battaglia TA 2012	●	●	?	?	+	+	+
Chen YC 2013	●	?	?	?	+	+	+
Clark CR 2011	●	●	?	?	●	+	+
Eli Ka 2002	●	●	?	?	+	+	●
Engelstad LP 2001	?	+	?	?	?	+	●
Fernández ME 2009	?	?	+	?	●	+	+
Markossian TW 2012	●	?	?	?	?	?	+
Miller SM 1997	+	+	+	+	?	+	?
Miller SM 2013	+	+	+	+	+	+	+
Percac-Lima S 2012	●	?	?	?	?	?	●

Figure 2. Risks of bias for each included study.

4.2 Types of intervention and its delivery modes

The intervention was termed “CM” only in five studies. The remaining five studies, where the interventions were named as patient navigation, telephone counselling, or care management, catered for inclusion criteria due to the contents of intervention similar to case management. Throughout this review, all interventions in included studies were unified as case management regardless of original names.

4.3 Mode of delivery of case management

Telephone-based case management was used in all ten studies included (Table 5). Furthermore, six trials applied face-to-face visits (Battaglia *et al.*, 2012; Chen *et al.*, 2013; Clark *et al.*, 2011; Ell *et al.*, 2002; Fernández *et al.*, 2009; Percac-Lima *et al.*, 2013); four studies performed telephone-based case management combined with appointment letters (Clark *et al.*, 2011; Engelstad *et al.*, 2001; Markossian *et al.*, 2012; Miller *et al.*, 1997); home visit was applied in two studies for in-depth assessment (Fernández *et al.*, 2009; Percac-Lima *et al.*, 2013); In five studies a protocol or manual was used to facilitate intervention implementation (Battaglia *et al.*, 2012; Fernández *et al.*, 2009; Markossian *et al.*, 2012; Miller *et al.*, 1997; Miller *et al.*, 2013).

4.4 Case management components

Case management in all studies comprised multiple components, some being part of a disease management programme (Battaglia *et al.*, 2012; Clark *et al.*, 2011; Ell *et al.*, 2002; Markossian *et al.*, 2012). Some had many components (Battaglia *et al.*, 2012; Chen *et al.*, 2013; Clark *et al.*, 2011; Ell *et al.*, 2002; Percac-Lima *et al.*, 2013) and others had fewer (Engelstad *et al.*, 2001; Fernández *et al.*, 2009; Markossian *et al.*, 2012; Miller *et al.*, 1997; Miller *et al.*, 2013).

The components of participant education were included in all trials (Table 6). One study described the case manager was in charge of dissemination of knowledge about occurrence and screening of cervical cancer, also providing information about medical resources available (Clark *et al.*, 2011). Case managers in five studies provided emotional or therapeutic support to patients and families, and provided advice regarding benefits and financial issues, such as supplying logistic support for transportation, housing, and food pantry service, or assisting patients to access public assistant programs (Battaglia *et al.*, 2012; Chen *et al.*, 2013; Clark *et al.*, 2011; Ell *et al.*, 2002; Percac-Lima *et al.*, 2013). Three studies (Battaglia *et al.*, 2012; Chen *et al.*, 2013; Fernández *et al.*, 2009) involved case management in terms of patient advocacy.

4.5 Effectiveness of case management interventions

The summary of overall effectiveness of study interventions was shown in Table 1.

Outcomes	OR (95% CI) (for dichotomous data)	No. of participants (studies)	Quality of the evidence (GRADE*)	Comments
Adherence to follow-up in six months	1.18 (0.83 to 1.67)	572 (4)	⊕⊕⊕⊕ High	No significant differences between groups; sensitivity analysis excluded one study which had high attrition, so the intervention group had significantly higher adherence rate
Adherence to follow-up in twelve months	3.23 (2.14 to 4.88)	707 (2)	⊕⊕⊕⊖ Moderate	Significant differences between groups with high heterogeneity
Adherence to follow-up over twelve months	HGSIL group: $\chi^2=11.9$; LGSIL group:	565 (1)	⊕⊕⊕⊖ Moderate	Significant differences between groups

	chi ² = 11			
The rate of follow-up completion	2.11 (1.09 to 4.10)	170 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Significant differences between groups; no significance between groups with ITT analysis
Diagnostic resolution in two months	2.18 (1.73 to 2.76)	2308 (2)	⊕ ⊕ ⊕ ⊖ Moderate	Significant differences between groups with high heterogeneity
Diagnostic resolution in twelve months	1.63 (1.34 to 1.98)	2308 (2)	⊕ ⊕ ⊕ ⊖ Moderate	Significant differences between groups with high heterogeneity
Diagnosis resolution within eighteen months in patients receiving follow-up within six months	4.4 (1.84 to 10.5)	108 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Significant differences between groups
Timely clinically indicated follow-up of abnormal results	1.18 (0.55 to 2.51)	108 (1)	⊕ ⊕ ⊕ ⊖ Moderate	No significant differences between groups
The rate of prolonged hospitalisation	1.43 (0.44 to 4.67)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	No significant differences between groups
The rate of nonadherence to treatment	3.69 (0.75 to 18.21)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	No significant differences between groups
The rate of patients to continue treatment in the same institute	2.76 (1.03 to 7.45)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Statistical differences between groups
The rate of unplanned hospital readmission	0.73 (0.25 to 2.2)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	No significant differences between groups
The rate of planned readmission for active treatment in fourteen days	5.27 (1.71 to 16.19)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Statistical differences between groups
The rate of planned readmission for active treatment in 15-30 days	4.85 (2.24 to 10.49)	200 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Statistical differences between groups
Time to diagnosis resolution	76/110 days	1763 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Intervention group: 76 days; Control group: 110 days
Time to initiation of colposcopy follow-up	127 → 120 days; 116 → 122 days	786 (1)	⊕ ⊕ ⊕ ⊖ Moderate	From 2004-2007 to 2008-2011, intervention group: ↓ 7 days; control group: ↑ 6 days
Directive cost of intervention	\$319	565 (1)	⊕ ⊕ ⊕ ⊖ Moderate	Per enrollee for one year of service
Patients satisfaction	97%	565 (1)	⊕ ⊕ ⊕ ⊖ Moderate	
Barriers to adherence to follow-up	Commercial insurance; higher literature; older age		⊕ ⊕ ⊕ ⊖ Moderate	
Patients' psychosocial		565 (1)	⊕ ⊕ ⊕ ⊖	45% women fearful of finding

construct			Moderate	cancer
<p>GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: Very uncertain about the estimate.</p>				

Table 1. Summary of findings

Four studies provided data about the proportion of participants who adhere to follow-up in six months (Engelstad *et al.*, 2001; Fernández *et al.*, 2009; Miller *et al.*, 1997; Miller *et al.*, 2013). There were no significant differences were found at this time point between groups (Figure 3; OR 1.18, 95% CI 0.83 to 1.67, n = 572, I² = 88%, P = 0.36). Due to high heterogeneity (I² = 88%, P = 0.36), a random-effect model was used for further analysis and still no significant differences between groups were found (Figure 4; OR 1.59, 95% CI 0.52 to 4.89, n = 572, I² = 88%, P = 0.42). Two studies reported that the intervention group had significantly higher adherence to follow-up (Engelstad *et al.*, 2001; Miller *et al.*, 1997). In one study, the differences between groups were not statistically significant although the adherence rate in case management group was higher than control group (Miller *et al.*, 2013). However, the adherence rate in intervention group was significantly lower than control group in the other study (Fernández *et al.*, 2009). Sensitivity analysis was performed and one study (Fernández *et al.*, 2009) was excluded due to high attrition and special targeted population (immigration farm workers). Then meta-analysis including three studies (Engelstad *et al.*, 2001; Miller *et al.*, 1997; Miller *et al.*, 2013) presented significant differences between groups (Figure 5; OR 2.64, 95% CI 1.61 to 4.31, n = 329, I² = 0%, P = 0.0001).

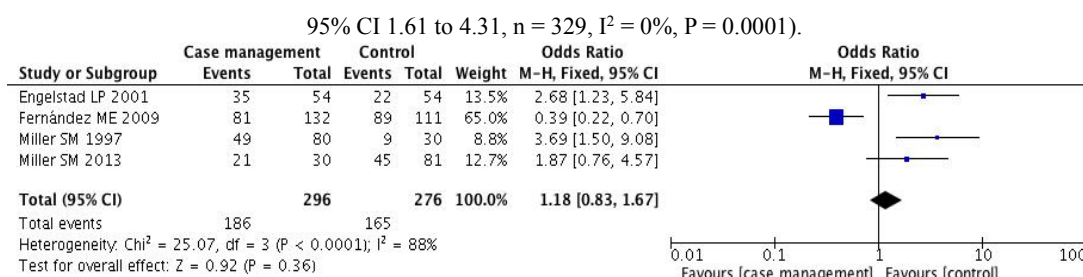


Figure 3. Forest plot of comparison: Adherence to follow-up in six months (fixed effect).

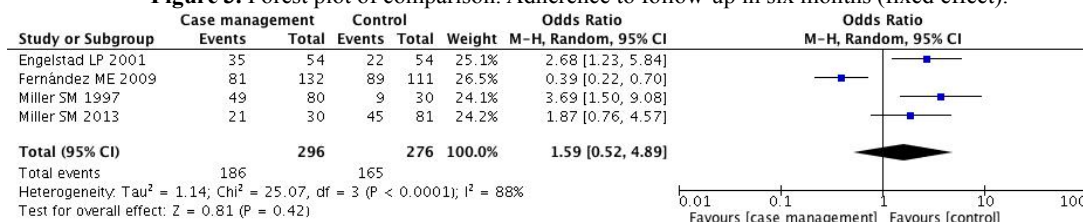


Figure 4. Forest plot of comparison: Adherence to follow-up in six months (random effect).

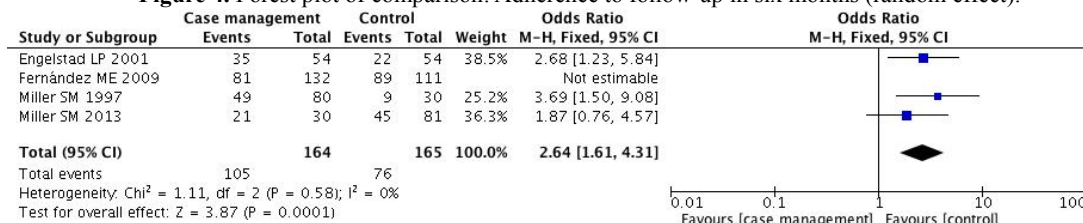


Figure 5. Forest plot of comparison: Adherence to follow-up in six months (heterogeneity excluded).

4.6 Adherence to follow-up in twelve months

The proportion of participants who adhere to follow-up in twelve months was reported in two studies with different conclusions (Ell *et al.*, 2002; Miller *et al.*, 2013). In one study (Ell *et al.*, 2002), significant differences were found between groups (P < 0.01), whereas in the other study (Miller *et al.*, 2013) there were no significantly higher

adherence rate in intervention group ($P = 0.46$). When the data were pooled, significant differences were found between groups at this time point (**Figure 6**; OR 3.23, 95% CI 2.14 to 4.88, $n = 707$, $I^2 = 93\%$, $P < 0.00001$). However, these data were highly heterogeneous ($I^2 = 93\%$, $P < 0.00001$). No significant differences were found between groups with a random-effect model (Figure 7; OR 1.93, 95% CI 0.29 to 12.59, $n = 707$, $I^2 = 93\%$, $P = 0.49$). The high heterogeneity arose from different study types of NRS (Ell *et al.*, 2002) and RCT (Miller *et al.*, 2013), the former embracing the shortcoming of sample selection, and the sample size

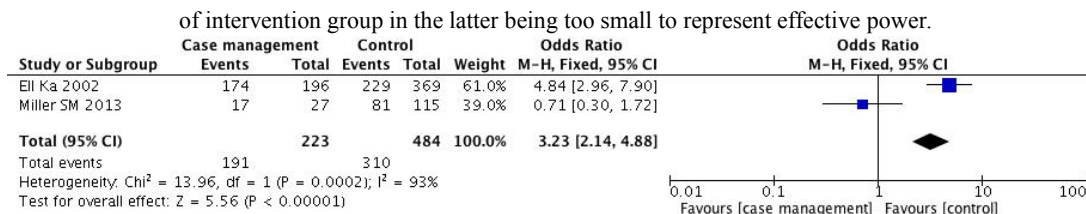


Figure 6. Forest plot of comparison: Adherence to follow-up in twelve months (fix effect).

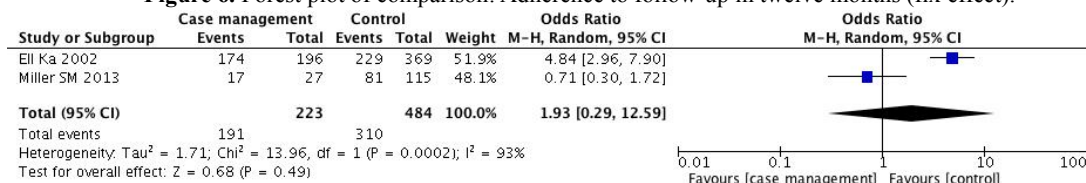


Figure 7. Forest plot of comparison: Adherence to follow-up in twelve months (random effect).

4.7 Adherence to follow-up over twelve months

Only one study (Ell *et al.*, 2002) reported adherence to follow-up over twelve months, and revealed a significant increase in the percentage of adherence to follow-up in the case management group in both high-grade squamous intraepithelial lesion (HGSIL) subgroup ($\chi^2 = 11.9$, $p = 0.001$) and low-grade squamous intraepithelial lesion (LGSIL) subgroup ($\chi^2 = 11$, $p = 0.004$). Data pooling could not be performed arising from no further data (such as OR and 95%CI) being provided.

4.8 The rate of follow-up completion

Data about completion rate of follow-up were available in one study (Fernández *et al.*, 2009). Case management group significantly promoted this outcome (**Figure 8**; OR 2.11, 95% CI 1.09 to 4.10, $n = 170$, $P = 0.03$). After intent-to-treat analysis ($n = 243$), significant differences were not found between groups (Figure 9; OR 1.37, 95% CI 0.74 to 2.55, $n = 243$, $P = 0.32$).

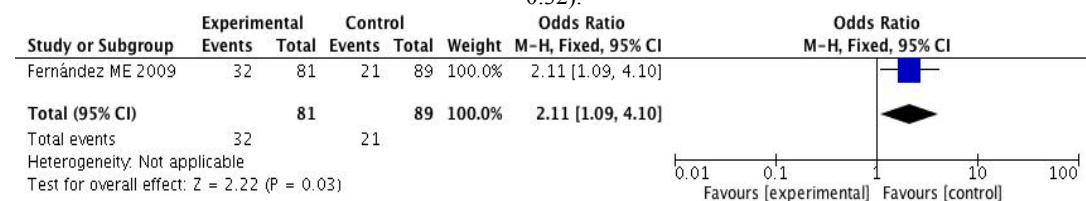


Figure 8. Forest plot of comparison: The rate of follow-up completion.

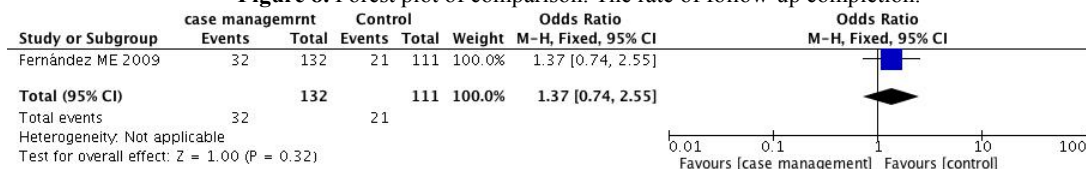


Figure 9. Forest plot of comparison: The rate of follow-up completion (with ITT analysis).

4.9 Time to diagnostic resolution

Diagnostic resolution within two months

Two studies provided data information at this time point (Battaglia *et al.*, 2012; Markossian *et al.*, 2012). In the

individual analyses, there were significant differences in both studies ($P < 0.001$). For pooled data, significant differences were also detected between groups, and intervention group showed higher rate of diagnostic resolution within two months (**Figure 10**; OR 2.18, 95% CI 1.73 to 2.76, $n = 2308$, $I^2 = 86\%$, $P < 0.00001$). However, the data presented high heterogeneity ($I^2 = 86\%$, $P < 0.00001$). With a random-effect model, the differences between groups were still statistically significant (Figure 11; OR 2.35, 95% CI 1.26 to 4.37, $n = 2308$, $I^2 = 86\%$, $P < 0.00001$). The sensitivity analysis was performed because high heterogeneity sustained. Two trials were similar in most of study design aspect, but one study (Battaglia *et al.*, 2012) had problems in allocation concealment, and the backgrounds of case managers were different as well.

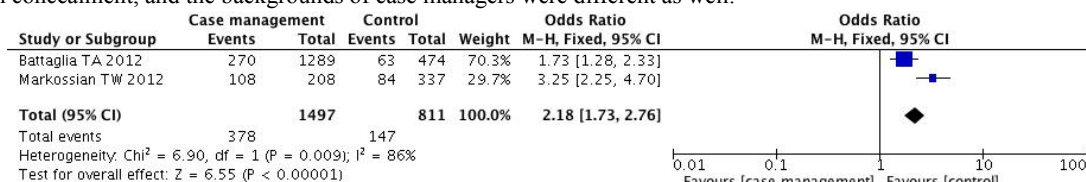


Figure 10. Forest plot of comparison: Diagnosis resolution within two months (fix effect).

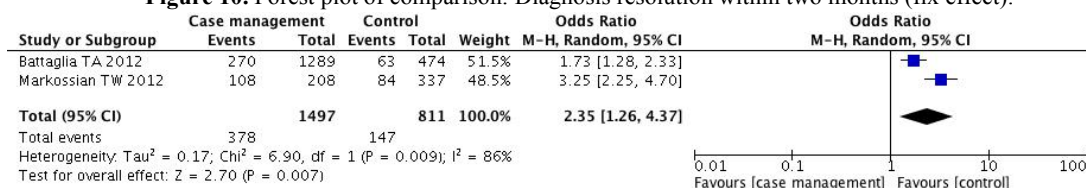


Figure 11. Forest plot of comparison: Diagnosis resolution within two months (random effect).

4.10 Diagnostic resolution within twelve months

Two studies provided data for this time point (Battaglia *et al.*, 2012; Markossian *et al.*, 2012). There were both significantly different between groups in the two studies when analysed individually ($P < 0.01$). For pooled data, significant differences were also observed between the intervention group and control group, and the former showed higher rate of diagnostic resolution within twelve months (**Figure 12**; OR 1.63, 95% CI 1.34 to 1.98, $n = 2308$, $I^2 = 90\%$, $P < 0.00001$). Nonetheless, due to high heterogeneity ($I^2 = 90\%$, $P < 0.00001$), a random-effect model was used, and no significant differences existed between groups (Figure 13; OR 2.06, 95% CI 0.91 to 4.7, $n = 2308$, $I^2 = 90\%$, $P = 0.08$).

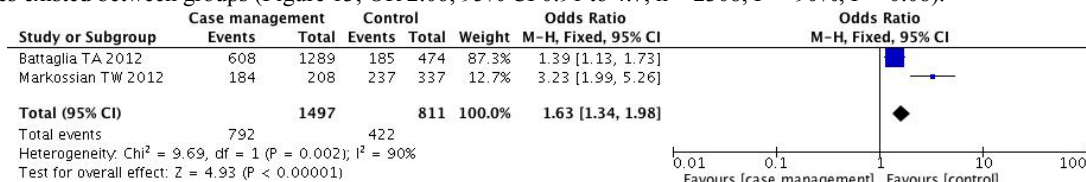


Figure 12. Forest plot of comparison: Diagnosis resolution within twelve months (fixed effect).

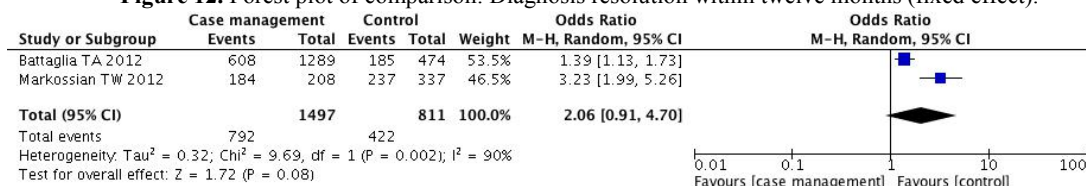


Figure 13. Forest plot of comparison: Diagnosis resolution within twelve months (fixed effect).

5. Discussion

In this review, evidence from four randomised controlled trials and six quasi-experimental studies with a total of 5980 participants were collated and summarised, comparing the effects of case management approaches on clinical outcomes in people with cervical cancer with usual care. Except for in two studies, the overall intervention duration ranged from 12 to 18 months. Nine of the studies included in this review came from the US, the rest one from Taiwan. The context where interventions were performed varied, including primary healthcare centres, public hospitals, and community clinics. To provide information for future research and practice in this field, the results have been

summarised in terms of diagnosis identification period and treatment period. In view of the amount of eligible trials being relatively small and the heterogeneity in the outcomes measured and time points, the conclusion was drawn only to a limited extent about the impact and optimum methodology of case management implementation. The main factors confining understanding as follows: insufficient cost and process assessment, the limitation in the similarity of interventions, and the methodological restrictions of the studies. These factors resulted in complexity of case management intervention, and called for studies with more rigorous methodology to evaluate both application and effectiveness.

5.1 Effectiveness of interventions during diagnosis identification

Significant increase was found in the intervention group in terms of adherence to follow-up in six months and over twelve months, diagnosis resolution in two months, twelve months and eighteen months. Case management brought on significant reduction in time to initiation of colposcopy follow-up and time to diagnosis resolution. No significant effects pro case management were found in timely clinically indicated follow-up of abnormal results. One study (Fernández *et al.*, 2009) reported a reduction of adherence rate to follow-up in intervention group in six months. The reasons were higher attrition rate resulting from extra time burden of participants for completion of data collect and more seasonal migration for farm work in the intervention group. Two studies reported different effects about adherence to follow-up in twelve months with one study finding significant differences between groups ($P < 0.01$) and the other not ($P = 0.46$). One study investigated direct cost of case management, and the result was \$319. But the cost only comprised personnel cost of the program service team, no travel and space expense in view of the nature of telephone intervention or in-clinic activities. Furthermore, the cost was based on the city with high labour cost. Therefore, the replicability and comparability of this figure were restricted.

5.2 Effectiveness of interventions during treatment period

In comparison to standard care, case management was more effective at the following items: the rate of patients to continue treatment in the same institute; the rate of planned readmission for active treatment in fourteen days; the rate of planned readmission for active treatment in 15-30 days. No statistical differences were found between groups in the rate of prolonged hospitalisation, but case management group with a higher rate due to patients' active cooperation to further therapy in the hospital. The case management intervention had a significantly higher rate of nonadherence to treatment, because with case management, the patients understood the treatment plan more clearly and had enough autonomy to make a decision.

5.3 Overall completeness and applicability of evidence

Four RCTs and six NRS were included in this review, and the majority of measured outcomes involved relatively small numbers of participants. In view of the popular coverage of this intervention in clinical practice, the application of case management in women with cervical cancer was not well investigated, especially for those in developing countries and regions. The authors of five studies were contacted to explore further information about measured outcomes and some additional details were acquired on the application of case management. Considering the diversity and complexity of interventions applied across included studies, the replication of interventions would be difficult in most instances. The possibilities of contamination were increased in the experimental circumstances due to scarcity of pre-existing professionals or teams. The intervention duration in most studies was over one year which was a reasonable time length for identify difference in intervention effects; two studies (Fernández *et al.*, 2009; Miller *et al.*, 1997) merely presented data at six months to keep low attrition rate but at the risk of precision reduction.

5.4 Limitations of this review

The conclusions should be treated with caution because there are several limitations to this review. First, the nature of a systematised review requires the review is finished by the student independently, which limits the precision, depth, and coverage of this review, because of the existence of procedures of literature searching, screening, bias evaluation

and data extraction where double researchers are asked. Second, although the number of included participants is high, the number of included studies is relatively low. Some true differences between groups may therefore have been missed. Finally, there is heterogeneity between the participants' demographics, types of cervical cancer, intervention components, delivery methods, outcome measures, and follow-up periods, which further limit the precision of the conclusions.

5.5 Implications for practice

5.5.1 For patients and carers

The care of cervical cancer is complicated due to its nature of diversity in clinical symptoms, treatment methods and outcomes of patients (Aubin *et al.*, 2012). Case management may represent a more patient-centred system of care. The available data suggested that, in diagnosis phase, adherence to follow-up and time to diagnosis at certain time points were improved through case management. In addition, during treatment period, satisfaction rate, adherence to continuing treatment in the same institute and planned readmission for active treatment were promoted in the intervention group, while the data did not indicate that case management decreased the rate of prolonged hospitalisation, nonadherence to treatment protocols, and unplanned hospital readmission.

5.5.2 For clinicians

The largely ambiguous findings may be explained by the substantial heterogeneity in the participants, interventions, and outcomes in the included studies. In this review, only 50% percent of included studies were applied case management in a comprehensive form. Some included trials evaluated case management following other changes of health system (e.g. improving adherence to recommended therapy plans); this may cause that some conclusions only applied to certain variants of case management packages. In future studies, the extent of intervention application according to original plan should be emphasised and reported. As proved by included studies, the replicability and fidelity of intervention could be improved by well-developed protocol manuals and training. Most included trials supported that the promotion of adherence rate to critical care processes could improve the service quality and clinical outcomes. Half of the ten studies were performed in primary care settings, and there was evidence for benefits from the combination of case management with primary care in people with cervical cancer. The rightly targeted population are crucially important to the effectiveness of interventions. Eight studies focused on low-income minority people who were proven to benefit considerably from case management.

5.5.3 For policy-makers

The application of case management on people with long-term conditions has been facilitated in some specialities, such as breast cancer and dementia (Iliffe *et al.*, 2014; Jennings-Sanders *et al.*, 2005). To establish a collaborative system of case management for people with long-term conditions, a series of health care policies were enacted in the UK since 2006 utilising the register data of Quality and Outcomes Framework from primary care (NICE 2006). In light of case management model, various interventions have been suggested for prevention and treatment of cervical cancer. For example, the American Surgeon Society (ASS) requires all institutes intending to acquire accreditation of ASS must perform case management in the screening and diagnosis phase. In the United States, case management serves as a co-ordinating role in cervical cancer care and this role was created based on current case management evidence. It is possible for case managers to facilitate the effective integration of primary care and specialised care services which is a tendency of current clinical practice.

This review shows that there is not yet a robust evidence base for the effectiveness of case management in meeting healthcare needs or cost effectiveness for patients or carers. Funders should support research which investigates the effectiveness of specific models of case management for patients with cervical cancer.

5.6 Implications for research

Further studies are needed to find out specific needs and investigate the effects of case management on different phases of cervical cancer. Outcome evaluation of case management is recommended to integrate with qualitative approaches to uncover the entire experiences of cancer patients (Tarasenko *et al.*, 2011).

It is notable that case management is much more popular in breast cancer region rather than cervical cancer. Most times the trials including cervical cancer cases were attached to the trials which mainly researched breast cancer, and high-quality trials, especially RCT, focusing exclusively on patients with cervical cancer are scarce, therefore, the studies exploring the effect of case management purely on patients with cervical cancer are extremely needed. Most included studies focused on low-sociodemographic people, but future studies should extend the coverage of population studied to diversity of cancer population other than only underserved groups. Heterogeneity in the studies, consisting of the diversity in methodologies, targeted people, intervention contents, outcome measures, has hampered determination of the overall effectiveness of case management. Rigorous methods and unequivocal outcome measures are thus required to validate the effects of case management.

Future studies of systematic reviews or meta-analyses could focus on comparison of the effectiveness of specific models of case management and usual care. The conclusions of this review would be intensified by additional evidence from high-quality, large-scale trials which investigate particular modalities and features of case management (e.g. face-to-face visit or telephone counselling). Future trials need to be rigorous in design and delivery, including high-quality descriptions of all aspects of methodology in the intervention and control groups in order to identify ingredients of this complicated approach, and facilitate the explanation and evaluation of study results. Future studies should also pay more attention to promote the precision of description about case manager identities, i.e. whether the role of case manager is set specialising in case management or only doing some activities of care coordination. Furthermore, future trials should also delineate precisely the core components and content of the intervention, and perform process evaluation throughout the research to effectively identify the ingredients of case management and appraise replicability and sustainability of the study. The classification of case management interventions according to the content and fidelity to the original intervention design is also important. To ensure the consistency, replicability and transparency of the complicated case management intervention, well-developed protocols and manuals should be popularised.

Matters are complicated by the various definitions about adherence to follow-up and timely diagnosis resolution, making meta-analysis more difficult. The same outcome was described by diverse measurements of high heterogeneity, causing difficulties in data transformation for researchers. The target of future research in this field should be set to provide data consistent with high-quality relevant literature. Thus far, few studies provided data about cost-effectiveness of case management. This gap, related to clinical benefits and cost savings for public health service system, should be addressed in future studies. Due consideration should be given to the perspectives of patient and carer about measuring psychological well-being, quality of life, social support, and satisfaction. The impact of diverse countries, culture, and acceptance and attitude of care should also be emphasised in future trials.

6. Conclusions

Relatively robust evidence is provided by several high-quality studies that case management improves clinical outcomes in cervical cancer at specified time points. Age, insurance status, literacy ability, and severity of abnormality affect the adherence to follow-up and treatment. Whereas in view of heterogeneity in the components of intervention and outcome measures across the included trials, more rigorously-designed studies are needed in the future to explore further cost-effective protocols of case managements maximising adherence to follow-up and treatment, and relevant barriers should be investigated further as well.

Author contributions

All authors contributed to the development of this manuscript. All authors reviewed and approved final manuscript prior to submission.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgements

The authors would like to acknowledge Ms Yingchun Zeng who provided many important suggestions to this paper.

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