UNIVERSITY OF THESSALY

SCHOOL OF MEDICINE

MASTER IN "BIOMEDICAL RESEARCH METHODOLOGY, BIOSTATISTICS AND CLINICAL BIOINFORMATICS"

Master Thesis

Assessing the quality of Randomized Controlled Trials examining the efficacy of Human Papilloma Virus (HPV) vaccines in cervical cancer prevention.

Αξιολόγηση της ποιότητας των τυχαιοποιημένων ελεγχόμενων δοκιμών που εξετάζουν την αποτελεσματικότητα των εμβολίων του ιού των ανθρωπίνων θηλωμάτων (HPV) για την πρόληψη του καρκίνου του τραχήλου της μήτρας.

Christina Thomopoulou

MSc Mathematician

Supervisor: George Bakalos

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Abstract

Introduction: The human papillomavirus (HPV) causes premalignant and malignant lesions of the cervix. The development of vaccines has helped to prevent diseases related to HPV. Randomized controlled trials (RCTs) are the gold standard by which health care professionals and others make decisions about treatment effectiveness.

Objective: Our objective was to assess the reporting quality of RCTs published the last 10 years, examining the efficacy of HPV vaccines in cervical cancer prevention using a standardized tool based on the Consolidated Standards of Reporting Trials (CONSORT) statement.

Methods: Quality was assessed according to the methodological items in the CONSORT statement. We searched one database, namely, Pubmed. Detailed quality coding was conducted on RCTs, published in English language, between 2006 and 2015. Reporting was evaluated overall, and for pre- and post-CONSORT periods.

Results: 19 of the 37 items (primary and secondary) were reported in less than 50% of the studies. After comparison of the two periods, a non-significant difference ($p>0.05$) was detected in all items.

Conclusion: The quality of the reports on RCTs of efficacy of hpv vaccines in cervical cancer prevention between 2006 and 2015 is moderate. Comparing two time periods, i.e. 2006-2009 and 2010-2015 we noticed there was a non-statistical significant improvement after CONSORT 2010 statement. Thus, researchers should be urged to conform to the CONSORT statement when reporting on RCTs.

Introduction

HPV is a group of more than 150 related viruses, more than 40 of which are typically transmitted through sexual contact and infect the anogenital region of males and females. In particular, HPV16 and HPV18 are known to cause around 70% of cervical cancer cases and the greatest risk of cervical cancer. HPV is a very common virus. Every year, over 27,000 women and men are affected by a cancer caused by HPV. Persistent HPV infection can cause cervical and other cancers. HPV vaccines are vaccines that are used to prevent HPV infection and therefore cervical cancer.

Randomized controlled trials (RCTs) are the gold standard by which health care professionals and others make decisions about treatment effectiveness. RCTs provide information for one clinical intervention compared with another. In randomized controlled trials (RCTs), the participants are allocated to two groups of interventions and control for the comparison of some outcomes between them. So, with the randomized controlled trials (RCTs) we can test the efficacy and effectiveness of HPV vaccines in cervical cancer prevention, which is a good design plan to assess the efficacy of vaccines.

The assessment of new drugs and treatments is important to the clinician in the selection of best therapy. Recent methodological analyses indicate the inadequate reporting and design are associated with biased estimates of treatment effects. So, decisions about some treatments are difficult. It is significant to differentiate between assessing the quality of a trial and the quality of its reporting. The quality of a trial focuses on design quality. The quality of a report can be defined as the provision of information about the design, conduct, and analysis of the trial.

In the mid-1990s, an international group of clinical trialists, statisticians, epidemiologists, and biomedical journal editors developed the Consolidated Standards of Reporting Trials (CONSORT) statement. The CONSORT statement includes a checklist and a flow diagram for reporting RCTs. The checklist is designed to help authors in the reporting of randomised controlled trials (RCTs). Since then, the checklist has experienced some changes. Further meetings of the Group in 1999 and 2000 led to the publication of the revised CONSORT statement 2001.

Following a meeting in January 2007, a further revision was developed and the CONSORT 2010 statement was published on March 24, 2010. The last CONSORT statement published in 2010, included 25 items.

We aimed to assess the quality of randomized controlled trials (RCTs) examining the efficacy of human papillomavirus vaccines in cervical cancer prevention according to the methodological items in the CONSORT statement 2010.

Methods

Studies Selection and Data Extraction

We have selected one database, namely, Pubmed to search all papers published between January 1, 2006 and 2015, with searching language limited to English. Selection of randomized controlled trials (RCTs) was made based on the appearance of the term “efficacy of hpv vaccines in cervical cancer prevention”. A total of 59 articles matched this search criteria. Of these, 5 were not published between 2006 and 2015, 1 was not published in English language, in 21 articles were not found free full texts and 9 were not relevant to topic. So, a final group of 23 RCTs was found. We have chosen all the RCTs concerning the efficacy of hpv vaccines in cervical cancer prevention. Among the selected, the intervention groups were treated with hpv vaccines. Figure I shows a flow chart for the selection of studies considered for inclusion.

A set of quality criteria for evaluating RCTs examining the efficacy of human papillomavirus (HPV) in cervical cancer prevention was compiled using criteria from the CONSORT Statement. The CONSORT statement of 2010 consists of 25 items (refined to 37 items, 25 primary and 12 secondary). According to the CONSORT 2010 checklist we created an evaluation form for each of the 25 items. The result of each item was assessed by yes (1 point) or no (0 point) depending whether the author had reported it.

Statistical Methods

Reporting was evaluated overall and in two publication periods, i.e. 2006-2009 (pre-CONSORT), and 2010-2015 (post-CONSORT).

Additional, reporting was evaluated checking if there is any difference between the journals which endorse CONSORT, compared to those they don't. Data were analyzed using Microsoft Excel 2007 and SPSS software (version 22.0, IBM SPSS). We counted the number of reports which met the standards of CONSORT 2010, and calculated the percentage of application of each standard. Also, we used parametric statistics and we compared pre- and post-CONSORT periods calculating the odds ratio (OR) and the respective 95% confidence interval using Fisher's exact test. A P-value <0.05 was considered statistically significant.

Table 1. Proportion of reporting of 25 data items in a total of 23 RCTs by publication period (pre- and post-CONSORT and combined)*

Data items	Combined†	Pre-CONSORT	Post-CONSORT	Odds Ratio and 95% CI ¥	p-value**
Title and Abstract					
1a	0.30(7)	0.14(1)	0.37(6)	3.6(0.35, 37.6)	0.37
1b	0.43(10)	0.14(1)	0.56(9)	7.7(0.75, 79.8)	0.09
Introduction					
Background and objectives					
2a	1.0(23)	1.0(7)	1.0(16)	-	-
2b	1.0(23)	1.0(7)	1.0(16)	-	-
Methods					
Trial design					
3a	0.48(11)	0.29(2)	0.56(9)	3.2(0.47, 21.8)	0.37
3b	0.04(1)	0.0(0)	0.06(1)	-	1.000
Participants					
4a	1.0(23)	1.0(7)	1.0(16)	-	-
4b	0.87(20)	0.86(6)	0.88(14)	1.17(0.088, 15.46)	1.000
Interventions					
5	0.83(19)	0.71(5)	0.88(14)	2.8(0.3, 25.5)	0.56
Outcomes					
6a	0.65(15)	0.43(3)	0.75(12)	4(0.6, 26.1)	0.18

6b	0.04(1)	0.0(0)	0.06(1)	-	1.000
Sample size					
7a	0.17(4)	0.0(0)	0.25(4)	-	0.27
7b	0.13(3)	0.14	0.13(2)	0.86(0.65, 11.36)	1.000
Randomisation					
Sequence generation					
8a	0.26(6)	0.29(2)	0.38(6)	0.83(0.1, 6.1)	1.000
8b	0.09(2)	0.14(1)	0.25(4)	0.4(0.21, 7.5)	0.53
Allocation concealment mechanism					
9	0.26(6)	0.29(2)	0.25(4)	0.83(0.1, 6.1)	1.000
Implementation					
10	0.0(0)	0.0(0)	0.0(0)	-	-
Blinding					
11a	0.30(7)	0.14(1)	0.38(6)	3.6(0.35, 37.6)	0.37
11b	0.26(6)	0.14(1)	0.31(5)	2.73(0.26, 29.1)	0.6
Statistical methods					
12a	1.0(23)	1.0(7)	1.0(16)	-	-
12b	0.57(13)	0.29(2)	0.69(11)	5.5(0.78, 38.7)	0.17
Results					
Participant flow					
13a	0.65(15)	0.57(4)	0.69(11)	1.65(0.26, 10.3)	0.66
13b	0.61(14)	0.57(4)	0.63(10)	1.25(0.21, 7.6)	1.000
Reqruitment					
14a	0.09(2)	0.0(0)	0.13(2)	-	1.000
14b	0.0(0)	0.0(0)	0.0(0)	-	-
Baseline data					
15	0.78(18)	0.71(5)	0.81(13)	1.7(0.22, 13.67)	0.62
Numbers analyses					
16	0.35(8)	0.14(1)	0.44(7)	4.67(0.45, 48.3)	0.35
Outcomes and estimation					
17a	1.0(23)	1.0(7)	1.0(16)	-	-
17b	0.04(1)	0.0(0)	0.06(1)	-	1.000

Ancillary analyses					
18	0.78(18)	0.71(5)	0.81(13)	1.7(0.22, 13.67)	0.62
Harms					
19	0.39(9)	0.43(3)	0.38(6)	0.8(0.13, 4.87)	1.000
Discussion					
Limitations					
20	0.7(16)	0.71(5)	0.69(11)	0.9(0.16, 6.2)	1.000
Generalisability					
21	0.78(18)	0.71(5)	0.81(13)	1.73(0.22, 13.67)	0.62
Interpretation					
22	0.65(15)	0.57(4)	0.69(11)	1.65(0.20, 10.3)	0.66
Other information					
Registration					
23	0.52(12)	0.43(3)	0.56(9)	1.7 (0.28, 10.3)	0.67
Protocol					
24	0.30(7)	0.29(2)	0.31(5)	1.14(0.16, 7.99)	1.000
Funding					
25	0.7(16)	0.86(6)	0.63(10)	0.28(0.03, 2.9)	0.37

*CONSORT=Consolidated Standards of Reporting Trials

†The percentage of articles reporting the CONSORT item

¥ Odds ratio of reporting an item at post-CONSORT period relative to pre-CONSORT.

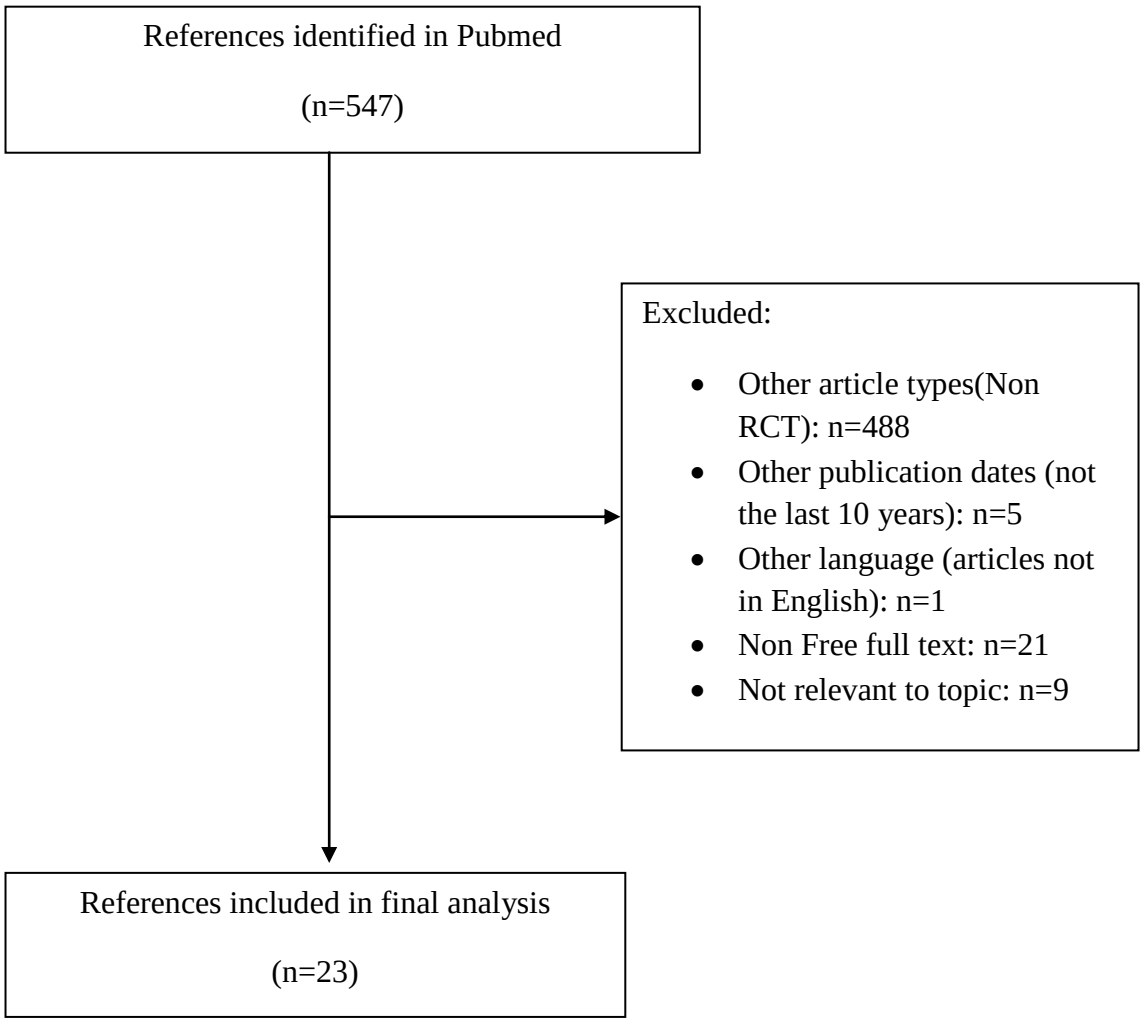
** p-values from Fisher's exact test for testing the association between reporting an item and publication period.

Combined: 2006-2015 (n=23)

Pre-CONSORT: 2006-2009 (n=7)

Post-CONSORT: 2010-2015 (n=16)

Figure I. Flow diagram showing selection of reports for inclusion in study



Results

Our database searching on PubMed identified 547 articles on the efficacy of human papillomavirus vaccines in cervical cancer prevention. Of these 524 were excluded for various reasons. Reasons for study exclusion are given in Figure I. In total, 23 RCTs were selected for analysis and quality assessment. Of these articles, 7 were published in the pre-CONSORT period (2006-2009) and 16 in the post-CONSORT period (2010-2015). The articles were retrieved from 13 journals of which 10 have not endorsed the CONSORT statement (Table 2).

The primary outcome of the study was the number and percentage of items on the CONSORT checklist that were reported between 2006 and 2015. The total number and percentage of RCTs reporting each quality criterion is provided in Table 1 and based on 25 standards of CONSORT 2010.

When the 23 RCTs are considered together, according to the 37 items in CONSORT 2010 checklist, only 4.3% (1/23) reported important changes to methods after trial commencement, changes to trial outcomes after the trial commenced and presentation of both absolute and relative effect sizes, 30.4% (7/23) mentioned ‘’randomization’’ in the title, blinding to interventions and where the full trial protocol can be accessed, 65.2% (15/23) reported completely defined pre-specified primary and secondary outcome measures, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome and trial interpretation, 78.3% (18/23) reported the baseline data with a table, ancillary analyses and Generalisability, 26.1% (6/23) reported the method used to generate the random allocation sequence, the Allocation concealment mechanism and the similarity of interventions, 8.7% (2/23) reported the type of randomisation and dates defining the periods of recruitment and follow-up, 69.6% (16/23) reported trial limitations and the source of funding, 60.9% (14/23) reported losses and exclusions after randomisation, 39.1% (9/23) reported side effects, 47.8% (11/23) reported description of trial design, 43.5% (10/23) reported structured summary, 87% (20/23) reported settings and locations where the data were collected, 82.6% (19/23) reported the interventions for each group, 17.4% (4/23) reported how sample size was determined, 13% (3/23) reported explanation of any interim analyses and stopping

guidelines, 56.5% (13/23) reported methods for additional analyses, 34.8% (8/23) reported the number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups and 52.5% (12/23) reported the registration number and name of trial registry. 5 of the 37 items (2a, 2b, 4a, 12a and 17a) were reported in all included articles, while 2 items (10 and 14b) were not mentioned at all. Table 3 shows the items reported less often (<25%) and more often (>75%).

After comparison of the two periods, a non-significant improvement ($p>0.05$) was detected in all items. All the items are the same likely to be reported pre- and post- CONSORT 2010 (see respective OR at table 1).

After comparison of the journals, we noticed there was a statistical significant difference ($p<0.05$) between the journals which endorse CONSORT, compared to those they don't only on 3 items (3a, 14a, 22) (see table 3).

Table 2: Distribution of papers by journal

Journal	Papers (%*)	Consort endorser†
Lancet Oncology	1(4.3%)	YES
The new England journal of medicine	2(8.7%)	NO
Clinical and Vaccine Immunology	2(8.7%)	NO
The BMJ	2(8.7%)	NO
Journal of the national cancer institute	2(8.7%)	YES
The official journal of the Japanese cancer association	1(4.3%)	NO
PLOS ONE	2(8.7%)	YES

International journal of cancer	2(8.7%)	NO
American journal of epidemiology	1(4.3%)	NO
Human Vaccines & Immunotherapeutics	1(4.3%)	NO
The journal of infectious diseases	3(13%)	NO
British journal of cancer	1(4.3%)	NO
Others	3(13%)	NO

Table 3. Items reported less often (<25%) and more often (>75%) and comparison between the journals which endorse CONSORT and Not.

Items	*Reported less often (<25%)*	*Reported more often (>75%)*	*p-value*
Title and Abstract			
1a			1.000
1b			0.127
Introduction			
2a		✓	-
2b		✓	-
Methods			
3a			**0.037<0.05**
3b	✓		1.000
4a		✓	-
4b		✓	0.0539
5		✓	0.539
6a			0.122
6b	✓		1.000
7a	✓		0.539
7b	✓		1.000
8a			1.000
8b	✓		1.000
9			1.000
10	✓		-
11a			0.621
11b			0.576
12a		✓	-
12b			0.339
Results			

13a			0.621
13b			1.000
14a	✓		**0.040<0.05**
14b	✓		-
15		✓	0.291
16			1.000
17a		✓	-
17b	✓		1.000
18		✓	0.291
19			0.611
Discussion			
20			1.000
21		✓	0.545
22			**0.033<0.05**
Other information			
23			0.640
24			0.621
25			1.000

Conclusion

There are some limitations to this study. This was a study based only on PubMed searching, in a 10-year period and only in English language. However, only 1 of the articles published in other language and 5 in other dates (not the last 10 years). So, the risk of bias is limited.

The quality of the reports on RCTs of efficacy of hpv vaccines in cervical cancer prevention between 2006 and 2015 is moderate. 9 key methodological items of the CONSORT statement seem poor (0-25%), 10 low (26%-50%), 8 fair (51%-75%) and 10 good (76%-100%). Also, we compared two time periods, i.e. 2006-2009 and 2010-2015. We noticed there was any statistical significant difference between pre- and post-CONSORT 2010 in studies examining the efficacy of hpv vaccines in cervical cancer prevention. So, there was a non-statistical significant improvement after CONSORT 2010 statement.

Generally, the checklist improves the scientific quality of RCTs by assisting authors in the planning, preparing and conducting of RCTs. In conclusion, within the limitations of this study, we have shown that greater attention to quality aspects of design and reporting of RCTs in efficacy of hpv vaccines in cervical cancer prevention is needed and the adoption of the CONSORT statement should be a first step. Thus,

researchers should be urged to conform to the CONSORT statement when reporting on RCTs in future.

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