e-ISSN:2320-3528
p-ISSN:2347-2286

Research & Reviews: Journal of Microbiology and Biotechnology

Human Mammary Tumor Virus (HMTV) Infection and Risk of Human Breast Cancer: An Adaptive Meta-Analysis for Case-Control Studies

Jong-Myon Bae*, Eun Hee Kim

Department of Preventive Medicine, Jeju National University School of Medicine, Jeju-do, Korea

Research Article

Received date: 18/01/2016
Accepted date: 12/03/2016
Published date: 28/03/2016

***For Correspondence**

Jong-Myon Bae, Department of Preventive Medicine, Jeju National University School of Medicine, Jeju-do, Korea, Tel: +82-64-755-5567

E-mail: jmbae@jejunu.ac.kr

Keywords: Breast neoplasms, Risk factor, Mammary tumor virus, MMTV-LV, Mouse mammary tumor virus-like virus, *Retroviridae* infection, Meta-analysis

ABSTRACT

Objective: There is ongoing debate about the association between Human Mammary Tumor Virus (HMTV) infection and breast cancer. A systematic review (SR) published in 2014 revealed that there was a statistically significant association. However, there was suspected duplication of the studies selected in that SR and it also presented the need for a more detailed subgroup analysis by region. Therefore, the present study repeated the meta-analysis with the addition of relevant papers published before October 2015.

Methods: Using the papers selected for the previous SR, a list was made of the references, and the "cited articles" and "similar articles" provided by PubMed. Of these, we only selected case-control studies that used PCR to detect the HMTV gene in tissue. The criterion for duplication was papers that showed identical researcher names or affiliated institutions. Among duplicated papers, the one with the largest number of samples was chosen. The meta-analysis was used to obtain summary odds ratio (SOR) and 95% confidence interval (CI).

Results: A total of 13 case-control studies were selected. The total number of the case and control groups was 1,878 and 1,204 persons, respectively. The results of the meta-analysis for these 13 papers showed that HMTV infection increased the risk of breast cancer (SOR=8.37, 95% CI: 2.29-23.39; I-squared = 98.4%).

Conclusion: In the sub-group analysis, there was statistical significance for North America, the Mediterranean, and Australia. The results of this study support the claim that HMTV infection increases the risk of human breast cancer.

INTRODUCTION

Worldwide, breast cancer has the highest incidence in women of all primary site cancers [1]. The incidence has also increased in Korean women during the previous ten years since the early detection mammography program was introduced [2]. In addition to a genetic predisposition, various environmental factors are also known to contribute to the development of breast cancer [3-5]. The fact that Asian women, including Korea, show a relatively younger age of breast cancer occurrence than Western women has been one basis for the emergence of theories of viral infection as a cause of breast cancer [6-10].

Mouse Mammary Tumor Virus (MMTV) was reported to cause breast cancer in mice by Bitter, in 1936 [11], making it the first known oncogenic virus in mammals [4]. Since then, there have been efforts to find out whether an analogous virus might cause human breast cancer (HBC) [9]. In 1995, Wang et al. [12] used a 660-bp sequence related to the MMTV *env* gene, and reported that 38.5% of HBC patients were positive for this sequence. As a result, this was named Human Mammary Tumor Virus (HMTV),

and its 95% homologous to MMTV [13-15]. Currently, the debate about whether HMTV is a cause of breast cancer is still ongoing [16], but Salmons and Gunzburg [17] summarized the evidence that would make HMTV a cause according to Koch's postulates. And a systematic review (SR) by Wang et al. [14] of 12 case-control studies published before October 2013 reported a summary odds ratio (SOR) 15.2 (95% confidence intervals, CI: 9.98-23.13).

But there are two potential issues with the meta-analysis and conclusions from that SR [14]. First, there is a suspicion that the data from the selected papers was duplicated. Of the 12 papers, the authors' names and affiliated institutions were identical for 2 US papers [12,18] and 4 Australian papers [19-22]. However, the source of the samples for these papers is unclear, and moreover, there is no description of whether these papers each tested different cancer tissues. If there is a sample overlap between papers, the results of a meta-analysis that does not take this into account could be over-estimated. In other words, the papers for the meta-analysis need to be reselected with attention to the possibility of duplication between papers from identical authors and institutions. Second, the SR [14] claimed that the risk of HMTV-related breast cancer was much higher in Western countries compared to Asia, but the meta-analysis included 11 papers from Africa and Western countries combined, and only 1 paper from Asia. To make a more valid claim about region-specific differences, the 11 papers from Africa and Western countries need to be further subdivided, and the search period needs to be extended to perform a re-analysis with additional papers. Therefore, in the present study, we aimed to perform an adaptive meta-analysis looking at the association between HMTV infection and human breast cancer, with an extended search period for papers published before October 2015.

MATERIALS and METHODS

Literature search and selection of relevant papers

Since this was a reanalysis of a previously published SR [14], we applied a hand search strategy [23-25], rather than an electronic search. Specifically, we searched the references from the papers selected by Wang et al. [14], and made a list of the "Cited articles" and "Similar articles" for each paper, as provided by PubMed (www.ncbi.nlm.nih.gov/pubmed). The dates of publication for the papers included in the list were up to October 2015.

The selection criteria were the same as Wang et al. [14] as case-control studies that used tissue samples and a polymerase chain reaction (PCR) detection method. Based on the titles and abstracts of the papers in the compiled list, the following three exclusion criteria were applied – papers with a different hypothesis, expert reviews or systematic reviews, and case reports. Among the papers remaining after this process, a further 4 exclusion criteria were applied – no HMTV detected for either the case group or the control group, non-tissue samples, not using a PCR method, and duplicated samples. Here, duplicated samples were defined as papers published by researchers affiliated with the same institution and, after dividing the results into paraffin-embedded tissue (PET) and fresh frozen tissue (FFT), the paper with the largest combined number of samples for the case and control groups was selected. After applying all the above 7 exclusion criteria, the remaining case-control studies were selected for the final analysis.

Statistical analysis

Two researchers were responsible for applying the exclusion criteria for each paper and extracting HMTV-related information-total number of samples and number of positive samples for the case group and the control group, by sample type; nationality of subjects; cell selection method; detection method; kinds of control tissue. Samples were divided by type into either PET or FFT, and then the number of HMTV-positive and HMTV-negative subjects in the case and control groups were used to obtain the OR and 95% CI for each study. Using the subjects' nationality, the studies were categorized into North America, South America, Australia, the Mediterranean, and Asia. Cell selection methods were divided into either section cut from tissue (SC) or laser microdissection (LM). HMTV infection detection methods were divided into 4 groups-PCR, nested PCR (N-PCR), semi-nested PCR (SN-PCR), and fluorescent-nested PCR (FN-PCR). Control tissue was defined as either normal breast tissue (NBT), breast fibro-adenoma (BF), or adjacent normal breast tissue away from tumor (ANBT).

The I-squared value (%) was used to evaluate heterogeneity in the meta-analysis, and summary odds ratio (SOR) and 95% CI were initially obtained for a random effects model. Egger's test for small-study effects was used to test for publication bias [26]. In the case of publication bias, a sensitivity analysis was performed, excluding studies that caused issues in the forest plot. Also, additional subgroup analyses were performed according to sample type, region, cell selection method, and PCR testing method, and these were compared with the results of the previous SR [14]. The statistical significance level was set at 5% and the Statistics program STATA version 14 (www.stata.com) was used.

RESULTS

Figure 1 displays the process of selecting papers for the final analysis through a literature search process. In order to determine the risk of breast cancer caused by HMTV, 50 references were acquired based on the previous SR [14], and a list of 593 "Cited articles" and "Similar articles" was compiled using PubMed. When the selection criteria were applied in order to these 643 papers, 28 case-control studies were obtained. Of these, (1) 5 papers [27-31] were excluded because HMTV gene could not be detected in either the case or control group, (2) 3 papers [32-34] were excluded because the test samples were not tissue-based, (3) 1 paper [35] that did not used PCR, (4), and 6 papers [12,21,36-39] that used duplicate samples.

e-ISSN:2320-3528
p-ISSN:2347-2286

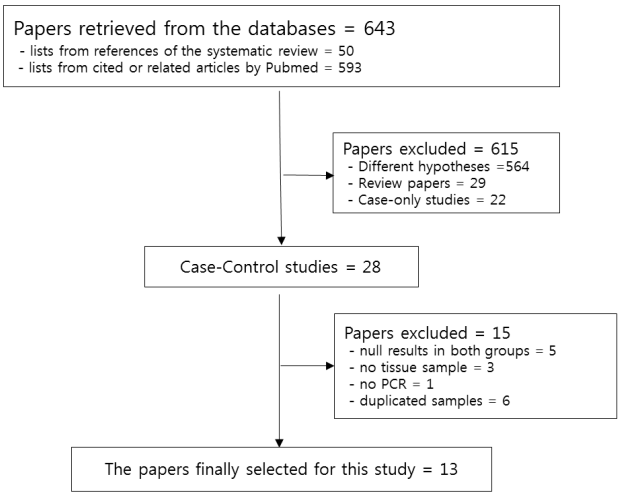

Figure 1. Flow chart of article selection.

The process of determining duplicate samples and excluding and selecting relevant papers is described in Table 1. Among research results for samples from the United States, there were a total of 6 papers [12,18,36-38,40] from the Mount Sinai School of Medicine, and of these, the papers with the largest total number of samples were Melena et al. [18] and Wang et al. [40], so these were included in the PET and FFT scores, respectively. There were also 5 papers [19-22,39] from the University of New South Wales in Australia, and of these, the results of Ford et al. [20] and Glenn et al. [22] were included in the scores for PET and FT respectively. The paper by Ford et al. in 2003 [19] used Vietnamese samples, and so was not excluded.

Table 1. Papers shown results of doubtfully overlapping samples by paraffin-embedded tissue (PET) and fresh frozen tissue (FFT).

Nation	Study	PET			FFT			Selected in Wang et al. [14]
		Target (bp)	Case	Control	Target (bp)	Case	Control	Y
US	Wang (1995) [12]	250	60/151	1/27	660	121/314	4/136	
	Pogh (1997) [36	250	60/151	1/28	660	131/335	2/150	
	Wang (1998) [37]				660	42730	0/10	
	Wang (2001) [38]				630	27/65	0/44	
	Melana (2001) [18]*	250	32/106	1/106				Y
	Wang (2001) [40]*				660/590	188/495	2/155	
Australia	Ford (2003) [19]	356	38/92	2/111				Y
	Ford (2004) [20]*	190	45/144	7/136				Y
	Ford (2004) [39]	356	26/33	0/20				
	Lawson (2010) [21]	255	33/74	0/29				
	Glenn (2012) [22]*				643	39/50	13/40	Y

*Articles selected for meta-analysis; Study: first author (year of publication) [reference number]

Following the above exclusion process, a total of 13 papers were selected for the meta-analysis [13,18-20,22,40-47]. Table 2 summarizes the 13 case-control studies in the final selection, together with the subjects' nationalities, cell selection methods, PCR methods, and the number of HMTV-positive individuals for each type of sample. In Ford et al. [20], data was only collected from females. From these 13 case-control studies, the total number of subjects in the case and control groups was 1,878 and 1,204, respectively. In terms of sample types, there were 6 studies for PET samples and 7 studies for FFT samples. By region, 3 studies were categorized as North America, 2 studies as South America, 2 studies as Australia, 4 studies as the Mediterranean coast, and 2 studies as Asia. For the cell selection method, 11 papers used sections cut from tissue and 2 papers used laser micro dissection. For the detection method, 4 papers used PCR, 6 papers used N-PCR, 2 papers used FN-PCR, and 1 paper used SN-PCR. In terms of control sample selection, 10 papers used NBT or BF, 2 papers used ANBT, and 1 paper used a combination of ANBT and NBT.

Table 2. Summary of the 13 selected case-control studies.

Study	Nation	PET			FFT			Cell selection	Detection	Matching Control
		Target (bp)	Case	Control	Target (bp)	Case	Control			
Melana (2001) [18]	US	250	32/106	1/106				SC	PCR	NBT
Wang (2001) [40]	US				660/590	188/495	2/155	SC	PCR	BF/NBT
Etkind (2000) [41]	US				660/250	27/73	0/35	SC	N-PCR	NBT
Ford (2004) [20]	Australia	190	45/144	7/136				SC	SN-PCR	BF/NBT

e-ISSN:2320-3528
p-ISSN:2347-2286

Glenn (2012) [22]	Australia				643	39/50	13/40	SC	N-PCR	NBT
Zammarchi (2006) [42]	Italy				248	15/45	0/8	LM	FN-PCR	NBT
Mazzanti (2011) [13]	Italy	202	47/69	5/46				LM	FN-PCR	NBT/ANBT
Hachana (2008) [43]	Tunisia				190	17/122	0/122	SC	N-PCR	NBT
Slaoui (2014) [44]	Morocco	171	24/42	6/18				SC	N-PCR	ANBT
Melana (2002) [45]	Argentina				250	23/74	1/15	SC	PCR	BF/NBT
Cedro-Tanda (2014) [46]	Mexico				660	57/458	72/458	SC	N-PCR	ANBT
Ford (2003) [19]	Vietnam	356	1/120	0/60				SC	N-PCR	NBT
Naushad (2014) [47]	Pakistan	660	16/80	0/5				SC	PCR	NBT

a) ANBT: Adjacent Normal Breast Tissue away from Tumor; BF: Breast Fibroadenoma; FFT: Fresh Frozen Tissue; FN-PCR: Fluorescent Nested Polymerase Chain Reaction (PCR); LM: Laser Microdissection; NBT: Normal Breast Tissue; N-PCR: Nested PCR; PET: Paraffin-Embedded Tissue; SC: Sections Cut from Tissue; SN-PCR: Semi-Nested PCR; Study: first author (year of publication) [reference number]

When the 13 papers were divided into PET and FFT, and a meta-analysis was performed applying an REM, the risk of SOR for HMTV-positive individuals was 7.96 for PET (95% CI: 3.37-18.84: I-squared=49.8%), and 9.82 for FFT (95% CI: 1.94-49.70: I-squared=90.1%) **(Figure 2).** An Egger test was performed to determine whether there was publication bias, and the p-values for PET and FFT were 0.763 and 0.019, respectively **(Table 3).** From the FFT studies in **Figure 2**, Cedro-Tanda et al. [46] was judged to be increasing heterogeneity and causing publication bias. When this was excluded, the publication bias disappeared (p=0.456), as did the heterogeneity (I-squared=21.9%). When this study was excluded from the FFT group, the SOR for the remaining 6 studies was 15.05 (95% CI: 6.49-34.91), and when combined with the PET group, the SOR for those 12 studies was 10.64 (95% CI: 4.95-20.30, I-squared=45.0%). Among detection methods, the SOR was highest for PCR, at 19.12 (95% CI: 5.34-68.47, I-squared=38.1%). Among control tissues, the SOR for the BF or NBT group was 12.04 (95% CI: 6.50-22.32, I-squared=20.7%), which was higher than the ANBT group.

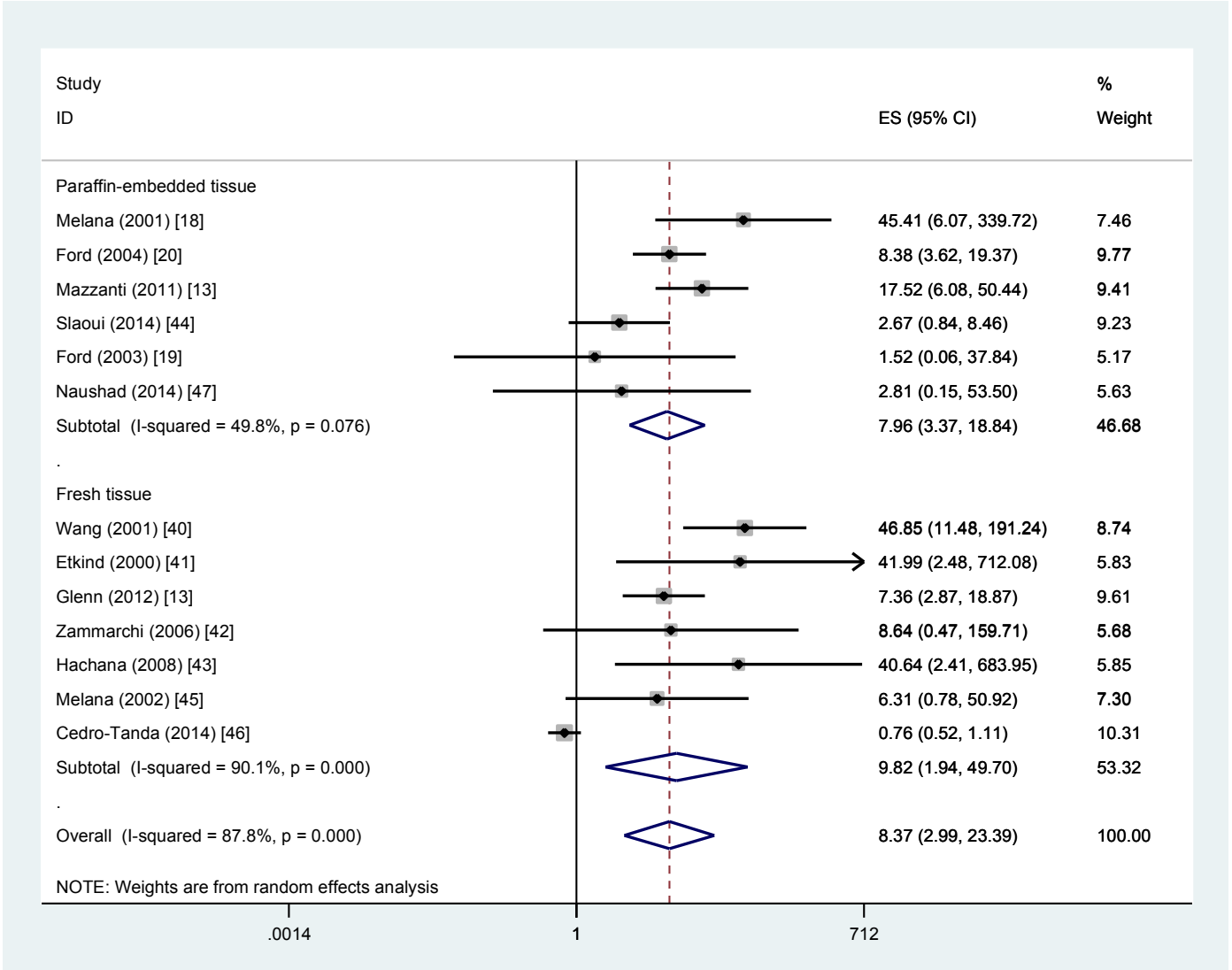

Figure 2. Forest plot using a random-effects summary estimate of 13 case-control studies by kinds of tissue. ID: author name (year of publication) [reference number]; ES : effect size; CI: confidence intervals.

Table 3. Sub-group analyses and sensitivity analyses by kinds of tissue and global area.

Study	Number of articles	Reference number	p-value of bias (Egger test)	I-squared (%)	SOR [95% CI]	SOR [95% CI] of Wang et al. [14]
Overall	13	13,18-20,40-47	0.007	98.4	8.37 [2.99, 23.39]	
PET	6	13,18,19,20,44,47	0.763	49.8	7.96 [3.37, 18.84]	14.95 [8.41, 26.55]
FFT	7	13,40-43,45,46	0.019	90.1	9.82 [1.94, 49.70]	
FFT except Ref [46]	6	13,40-43,45	0.456	21.9	15.05 [6.49, 34.91]	15.46 [8.37, 28.56]
All except Ref [46]	12	13,18-20,40-45,47	0.669	37.7	10.64 [5.89, 19.21]	15.20 [9.98, 23.13]
North America	3	18,40,41	0.113	0	45.72 [15.72, 132.99]	
South America	2	45,46	-	73.8	1.69 [0.23, 12.61]	
Australia	2	20,22	-	0	7.91 [4.23, 14.80]	
Mediterranean	4	13,42-44	0.75	56.2	9.29 [2.58, 33.39]	
Asia	2	19,47	-	0	2.12 [0.24, 18.64]	
SC	11	18-20,40,41,43-47	0.011	87.9	7.69 [2.52, 23.43]	
SC except Ref [46]	10	18-20,40,41,43-45,47	0.566	45.0	10.03 [4.95, 20.30]	15.15 [9.58, 23.94]
LM	2	13,42	-	0	16.14 [5.97, 43.61]	15.52 [5.57, 43.29]
PCR	4	18,40,45,47	0.179	38.1	19.12 [5.34, 68.47]	14.99 [8.34, 26.94]
N-PCR	6	19,41,22,43,44,46	0.062	85.2	4.46 [1.14, 17.50]	
N-PCR except Ref [46]	5	19,41,22,43,44	0.549	37.0	6.60 [2.44, 17.90]	43.31 [8.46, 221.74]
FN-PCR	2	13,42	-	0	16.14 [5.97, 46.61]	15.52 [5.57, 43.29]
SN-PCR	1	20	-	-	8.38 [3.62, 19.37]	8.38 [3.62, 19.37]
NBT or BF	10	18-20,22,40-43,45,47	0.44	20.7	12.04 [6.50, 22.32]	
NBT	7	18,19,22,41-43,47	0.42	8.4	10.77 [4.97, 24.20]	
ANBT	2	44,46	-	75.5	1.26 [0.38, 4.19]	
NBT & ANBT	1	13	-	-	17.52 [6.08, 50.44]	

ANBT: adjacent normal breast tissue away from tumor; BF: breast fibroadenoma; FFT: frozen tissue; FN-PCR: fluorescent nested polymerase chain reaction (PCR); LM: laser microdissection; NBT: normal breast tissue; N-PCR: nested PCR; PET: paraffin-embedded tissue; Ref [46]: the article by Cedro-Tanda et al. with reference number 46; SC: sections cut from tissue; SN-PCR: semi-nested PCR; Study: first author (year of publication) [reference number]

DISCUSSION

The meta-analysis of 13 case-control studies revealed that HMTV infection increases the risk of breast cancer. After excluding one Mexican study [46] that caused publication bias and heterogeneity the SOR was 10.64 (95% CI: 5.89-19.21), which was lower than the SOR given by Wang et al. [14], but still showed statistical significance. This is because the Mexican study [46] had the largest number of samples among the 13 studies and showed a higher positivity rate for control tissues (15.7%) than cancer tissues (12.4%). However, that study chose ANBT as the control tissue. Three [13,44,46] of the total 13 studies used ANBT as the control tissue, and after excluding Mazzanti et al. [13], which also used NBT, the remaining 2 studies both had an OR of less than 3 and did not show statistical significance **(Figure 2).** Hence, care should be taken when interpreting the result of studies using ANBT as the control tissue, and so we performed a sensitivity analysis centered on the relevant studies **(Table 3).**

Excluding the Mexican study [46], studies using FFT samples showed a higher SOR than studies using PET samples (15.05 *vs* 7.96). When compared with the previous SR **(Table 3)**, there was a 50% for PET studies (7.96 *vs* 14.95), and almost no change in FFT studies (15.05 *vs* 15.46). Additional research is required to determine whether this difference is the result of over-estimation due to duplicate analysis, or if it is the result of an actual difference between PET and FFT. Among PCR testing methods, N-PCR showed a large change compared to the previous SR (6.60 *vs* 43.31). Given that there were 3 N-PCR studies in the previous SR [14], while the present SR analyzed 6 N-PCR studies, this result can be interpreted as the present SR having obtained a more accurate value.

In the analysis by region, there was no statistical significance for Asia and South America. This could be interpreted as simply the result of having only 2 studies from each region, but Australia also only had 2 studies in this SR and still showed statistical significance. Hence, it is more valid to view this as an interregional difference in the risk of breast cancer due to HMTV infection. The highest risk was shown for North America, followed by the Mediterranean, then Australia, meaning that the theory of Stewart et al. [48] linking the incidence of human breast cancer to the natural ranges of mice. This theory has epidemiological significance

in that it can explain the results of immigrant studies that have shown an increase in breast cancer incidence among females who move from low-incidence to high-incidence regions [15].

The main limitation of the present SR is that duplicate samples were defined as studies with identical author names and affiliated institutions. In the previous SR [14], duplicate studies were defined as those with the clearest descriptions, and accordingly that SR only selected Wang et al. [12] among US studies. Meanwhile, the present SR selected Melana et al. [18] and Wang et al. [40], which had the most samples, and so it could be considered that there was no difference between the SRs in terms of duplication. Conversely, among Australian studies, the previous SR selected 3 PET studies [19-21], while the present SR only selected the 2004 study [20] from these, because it had the largest number of samples. In other words, only the selection of Australian studies showed a difference with the previous SR. The criteria for dealing with duplication in the present study can be viewed as stricter than the previous SR [14], and as a result, the risk was slightly lower but it still maintained statistical significance. Even in the excluded studies in **Table 1** were not actually duplicates, it is expected that there would be no change in the statistical significant of the risk of breast cancer due to HMTV.

Meanwhile, the following sentence from Wang et al. in 2001 [40] clearly shows that the 1995 and 1998 studies [12,37] both used the same samples: "DNA was extracted from fresh or frozen primary human breast carcinomas, and human breast cancer cell lines as described in previous publications". However, several studies shown in **Table 1** did not have a sufficient description of the source of the samples, and did not clearly demonstrate differences with previous published samples. In the future, emphasis needs to be placed on reflecting the above information in the research methods.

Because the present SR aimed to resolve the doubts regarding the previous SR [14], a hand search was preferred over a new electronic search, since this made maximal use of the results of the previous SR. Consequently, we were able to acquire an additional 3 papers published after November 2013 [44,46,47]. The papers acquired through the selection process in this study can be used as an important list for future adaptive meta-analyses.

In conclusion, this SR selected 13 case-control studies by lengthening the publication period and reassessing sample duplication, and the results supported the claim that HMTV infection increases the risk of human breast cancer. In order to end the debate, additional research is required into the oncogenic mechanisms of HMTV infection [9,46]. This is because an understanding of the oncogenic process would enable suitable diagnosis, development of treatments that improve prognoses, and the design of more active prevention strategies [47]. In particular, given that human papillomavirus and Epstein-Barr virus have also been discovered in HBC tissue as well as HMTV [9], vaccine development may present a new opportunity for breast cancer management [49].

ACKNOWLEDGEMENT

This study was supported by a grant from the Korean Foundation for Cancer Research, Seoul, and Republic of Korea (2013-2). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no competing interests exist.

REFERENCES

1. Jemal A, et al. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
2. Jung KW, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015; 47: 127-141.
3. Jung SJ, et al. Association of selected medical conditions with breast cancer risk in Korea. J Prev Med Public Health 2013; 46: 346-352.
4. Mason AL, et al. Mouse mammary tumor virus in human breast cancer red herring or smoking gun? Am J Pathol 2011; 179: 1588-1590.
5. Dumitrescu RG and Cotarla I. Understanding breast cancer risk -- where do we stand in 2005? J Cell Mol Med 2005; 9: 208-221.
6. Curado MP. Breast cancer in the world: incidence and mortality. Salud Publica Mex 2011; 53: 372-384.
7. Shin HR, et al. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. Cancer Causes Control 2010; 21: 1777-1785.
8. Bae JM. Two hypotheses of dense breasts and viral infection for explaining incidence of breast cancer by age group in Korean women. Epidemiol Health 2014; 36: e2014020.
9. Alibek K, et al. Role of viruses in the development of breast cancer. Infect Agent Cancer 2013; 8: 32.
10. Floor SL, et al. Hallmarks of cancer: of all cancer cells, all the time? Trends Mol Med 2012; 18: 509-515.
11. Bittner JJ. Some possible effects of nursing on the mammary gland tumor incidence in mice. Science 1936; 84: 162.

12. Wang Y, et al. Detection of mammary tumor virus env gene-like sequences in human breast cancer. Cancer Res 1995; 55: 5173-5179.

13. Mazzanti CM, et al. A mouse mammary tumor virus env-like exogenous sequence is strictly related to progression of human sporadic breast carcinoma. Am J Pathol 2011; 179: 2083-2090.

14. Wang F, et al. Mouse mammary tumor virus-like virus infection and the risk of human breast cancer: a meta-analysis. Am J Transl Res 2014; 6: 248-266.

15. Brower V. Mouse mammary tumor virus: new tumor virus or just a rumor virus? J Natl Cancer Inst 2009; 101: 293-295.

16. Lawson JS, et al. Viruses and human breast cancer. Future Microbiol 2006; 1: 33-51.

17. Salmons B and Gunzburg WH. Revisiting a role for a mammary tumor retrovirus in human breast cancer. Int J Cancer 2013; 133: 1530-1535.

18. Melana SM, et al. Search for mouse mammary tumor virus-like env sequences in cancer and normal breast from the same individuals. Clin Cancer 2001; Res 7: 283-284.

19. Ford CE, et al. Mouse mammary tumor virus-like gene sequences in breast tumors of Australian and Vietnamese women. Clin Cancer Res 2003; 9: 1118-1120.

20. Ford CE, et al. Progression from normal breast pathology to breast cancer is associated with increasing prevalence of mouse mammary tumor virus-like sequences in men and women. Cancer Res 2004; 64: 4755-4759.

21. Lawson JS, et al. Mouse mammary tumor virus-like sequences in human breast cancer. Cancer Res 2010; 70: 3576-3585.

22. Glenn WK, et al. Epstein-Barr virus, human papillomavirus and mouse mammary tumour virus as multiple viruses in breast cancer. PLoS One 2012; 7: e48788.

23. Bae JM. Narrative reviews. Epidemiol Health 2014; 36; e2014018.

24. Bae JM. Human papillomavirus 16 infection as a potential risk factor for prostate cancer: an adaptive meta-analysis. Epidemiol Health 2015; 37: e2015005.

25. Bae JM and Kim EH. Hormone Replacement Therapy and Risk of Breast Cancer in Korean Women: A Quantitative Systematic Review. J Prev Med Public Health 2015; 48: 225-230.

26. Harbord RM, et al. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006; 25: 3443-3457.

27. Morales-Sánchez A, et al. No association between Epstein-Barr Virus and Mouse Mammary Tumor Virus with breast cancer in Mexican women. Sci Rep 2013; 3: 2970.

28. Bindra A, et al. Search for DNA of exogenous mouse mammary tumor virus-related virus in human breast cancer samples. J Gen Virol 2007; 88: 1806-1809.

29. Frank O, et al. Variable transcriptional activity of endogenous retroviruses in human breast cancer. J Virol 2008; 82: 1808-1818.

30. Fukuoka H, et al. No association of mouse mammary tumor virus-related retrovirus with Japanese cases of breast cancer. J Med Virol 2008; 80: 1447-1451.

31. Ahangar Oskouee M, et al. No evidence of mammary tumor virus env gene-like sequences among Iranian women with breast cancer. Intervirology 2014; 57: 353-356.

32. Malivanova TF, et al. Humoral antibodies to structural proteins of murine mammary tumor virus as a potential immunologic marker of human breast cancer. Vopr Onkol 1995; 41: 43-46.

33. Riabykh TP, et al. Correlation of MMTV antibody expression and risk factors of human breast cancer. Vopr Onkol 1996; 42: 40-45.

34. Kriukova IN, et al. An antigen related to the mouse mammary cancer virus env gene product, detected in human lymphocytes, is associated with human breast cancer. Mol Gen Mikrobiol Virusol 2001; 2: 37-41.

35. Hughes G, et al. Are retroviruses involved in the aetiology of human breast cancer? Cancer Lett 1996; 103: 219-225.

36. Pogo BG and Holland JF. Possibilities of a viral etiology for human breast cancer: A review. Biol Trace Elem Res 1997; 56: 131-142.

37. Wang Y, et al. Expression of mouse mammary tumor virus-like env gene sequences in human breast cancer. Clin Cancer 1998; Res 4: 2565-2568.

38. Wang Y, et al. Detection of MMTV-like LTR and LTR-env gene sequences in human breast cancer. Int J Oncol 2001; 18: 1041-1044.

39. Ford CE, et al. Mouse mammary tumor virus-like RNA transcripts and DNA are found in affected cells of human breast cancer. Clin Cancer Res 2004; 10: 7284-7289.

40. Wang Y, et al. MMTV-like env gene sequences in human breast cancer. Arch Virol 2001; 146: 171-180.

41. Etkind P, et al. Mouse mammary tumor virus-like ENV gene sequences in human breast tumors and in a lymphoma of a breast cancer patient. Clin Cancer 2000; Res 6: 1273-1278.

42. Zammarchi F, et al. MMTV-like sequences in human breast cancer: a fluorescent PCR/laser microdissection approach. J Pathol 2006; 209: 436-444.

43. Hachana M, et al. Prevalence and characteristics of the MMTV-like associated breast carcinomas in Tunisia. Cancer Lett 2008; 271: 222-230.

44. Slaoui M, et al. Detection of MMTV-Like sequences in Moroccan breast cancer cases. Infect Agent Cancer 2014; 9: 37.

45. Melana SM, et al. Detection of murine mammary tumor virus (MMTV) env gene-like sequences in breast cancer from Argentine patients. Medicina 2002; 62: 323-327.

46. Cedro-Tanda A, et al. Prevalence of HMTV in breast carcinomas and unaffected tissue from Mexican women. BMC Cancer 2014; 14: 942.

47. Naushad W, et al. Detection and identification of mouse mammary tumor virus-like DNA sequences in blood and breast tissues of breast cancer patients. Tumour Biol 2014; 35: 8077-8086.

48. Stewart TH, et al. Breast cancer incidence highest in the range of one species of house mouse, Mus domesticus. Br J Cancer 2000; 82: 446-451.

49. Marrão G, et al. Epstein-Barr virus infection and clinical outcome in breast cancer patients correlate with immune cell TNF-α/IFN-γ response. BMC Cancer 2014; 14: 665.