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HLA-DRB1 alleles and cervical cancer: A meta-analysis of 36 case-control studies

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ABSTRACT

Background: Human leukocyte antigens (HLA) are encoded by closely linked genetic loci, and are important in cervical carcinogenesis. The association between HLA-DRB1 alleles with cervical cancer has been studied extensively, but results reported thus far have been inconsistent. Hence, we performed a meta-analysis to precisely assess this association.

Methods: A literature search was conducted in various online databases to identify suitable articles. Case-control studies investigating the association between HLA-DRB1 alleles and cervical cancer were included in this study. Fixed and random-effect models were used to calculate the pooled odds ratio (OR) and 95% confidence intervals (CIs).

Results: A total of 6645 cases and 9095 controls from 36 case-control studies were included. Of the 13 HLA-DRB1 family alleles, DRB1*09 (OR = 1.30) and DRB1 *15 (OR = 1.60) were associated with cervical cancer risk, whilst DRB1*13 (OR = 0.66) exerted a protective effect. Among the 44 HLA-DRB1 specific alleles, DRB1*04:01 (OR = 1.25), DRB1*10:01 (OR = 1.45), DRB1*11:01 (OR = 1.32), DRB1*15:01 (OR = 1.21) and DRB1*15:02 (OR = 1.55) were associated with an increased risk of cervical cancer. However, DRB1*04:06 (OR = 0.52), DRB1*12:02 (OR = 0.61), DRB1*13:01 (OR = 0.62), DRB1*13:02 (OR = 0.57), and DRB1*14:04 (OR = 0.37) were associated with a decreased risk of cervical cancer. Subgroup analysis also revealed that HLA-DRB1 alleles are associated with cervical cancer in Asian, Caucasian, Hispanic or Latin American and black sub-Saharan Africa populations.

Conclusion: Our meta-analysis revealed that multiple HLA-DRB1 alleles are associated with cervical cancer in women of diverse ancestry populations.

1. Introduction

The burden of cervical cancer is highest in developing regions of the world, especially in sub-Saharan Africa and South-Asia [1] where it is estimated that nearly 25 million cervical cancer cases will occur in the next five decades [2]. Cervical cancer is the second most common gynaecological malignancy among women and it has primarily been associated with oncogenic human papillomavirus (HPV) infection [3]. HPV plays an important role in cervical carcinogenesis and is found in about 96% of all cervical tumours [4,5]. However, the majority of HPV infected patients clear the infection within two years after exposure [6]. This suggests that host immune surveillance is critical in the clearance and regression of HPV infection.

The ability to spontaneously clear and regress the HPV infection usually depends on the immune-competence of the host [7]. Previous studies have indicated that polymorphisms of the immune response genes have a great influence on the outcome of HPV infection [8–10]. Human leukocyte antigen (HLA), located on chromosome 6, encodes genes that are crucial in the immune response to pathogens. The HLA class I and II bind and present pathogens to CD8 and $CD4^+$ T cells, respectively [11]. The HLA class II encodes DQ, DP and DR genes which are crucial in the presentation of exogenous antigen to the immune cells to initiate cell-mediated immune responses. Among the HLA class II genes, HLA-DRB1 is the most polymorphic and it has been associated

Abbreviations: HPV, human papillomavirus; HLA, human leukocyte antigen; NOS, Newcastle-Ottawa scale; OR, odds ratio; CI, confidence interval; P_{het}, *P*-value for heterogeneity

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with HPV persistence, pre-invasive cervical lesions and cervical cancer [12]. One of the earliest studies to investigate this association reported that HLA-DRB1 alleles are associated with cervical cancer risk [13]. Later, more than 58 studies have investigated this association over the years and results reported thus far have been inconsistent. The lack of consistency observed in previous studies may be due to genetic variation of the human population across the world and the small sample sizes from individual studies, which significantly reduced the statistical power to detect this association.

To address this, a meta-analysis was conducted in the Han Chinese population and found significant associations between HLA-DRB1 alleles with cervical cancer [14]. However, this meta-analysis included only 12 early case-control studies, and results reported cannot be generalized to other ethnic populations. Moreover, recent studies are needed to address the methodological issues observed in previous studies such as the use of low HLA typing resolution. Therefore, we conducted a meta-analysis of 36 studies to assess this association. Subgroup analysis was performed in individuals who share similar genetic backgrounds and environmental exposures. This allowed us to rule out confounding of our results from local environmental exposure and identify ancestry-specific alleles that can be used to identify women at high risk of cervical cancer in different ethnicities.

2. Methods

2.1. Identification of relevant studies

We identified relevant studies in various online databases including PubMed, Elsevier Science, Medline, and Google scholar using the following search terms “HLA-DRB1” or “HLA class II”, “polymorphism” and “cervical cancer” or “cervical neoplasia” or “carcinoma” or “cervix”. We sought to identify all case-control studies investigating this association and we also searched the internet for unpublished data. We also reviewed the references of the eligible articles to identify other potentially relevant articles. A literature search was conducted until no further suitable articles were found in the database. The meta-analysis study was performed according to PRISMA guidelines [15].

2.2. Selection criteria

The study inclusion criteria for the current meta-analysis were: (i) studies investigating the association between HLA-DRB1 alleles and cervical cancer, (ii) case-control studies, (iii) studies presenting original data, (iv) studies that provided the frequencies of HLA-DRB1 alleles in both cases and controls, and (v) studies published in English. We excluded studies that were: (i) duplicate or repetitive report (ii) family-based designed, (iii) raw data not available to retrieve, and (iv) case report, case series, editorial, review, and conference abstract. In case of some studies reported in the same ancestry population the most recent one or the one with the largest sample size was selected.

2.3. Quality assessment and data extraction

The Newcastle-Ottawa Scale (NOS) was used to quantify the quality of each study [16]. The total score on the NOS was nine stars and all studies that scored > 5 stars were considered to have high quality and included in the data analysis. Data were extracted from all the eligible full-text articles in Asians [17–31], Caucasians [32–40], Hispanic or Latin Americans [41–47] and black sub-Saharan Africans [48,49], North-Africans in Tunisia [50], the Middle East in Iran [51] and from mixed population in Canada [52] by two independent authors using the aforementioned study selection criteria. From these studies, we extracted names of the first authors, year of publication, countries where the study was originally conducted, the HLA typing methods used, ethnicity, and distribution of HLA-DRB1 alleles in both cases and controls. In case of discrepancies between the two authors, a consensus was reached through discussion.

2.4. Statistical analysis

Cervical cancer risk was calculated using odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were determined using the Z-test. The I^2 squared and Cochrane’s Q statistic tests were used to quantify heterogeneity of included studies. A random-effect model was performed when *p*-value for heterogeneity was significant at $P_{het} < 0.01$ or I^2 of > 50%. However, when the *p*-value was not statistically significant at $P_{het} > 0.01$ or I^2 of ≤ 50%, the ORs and 95%CI from each study was calculated using the fixed-effect model. Subgroup analyses were also performed in the Asians, Caucasians, Hispanic or Latin Americans and black sub-Saharan Africans. The robustness of our results was tested by sensitivity analysis, where one study at a time was excluded in the model to assess the stability of the overall ORs and 95% CI. Since studies that report null association are less likely to be published, a Begg’s funnel plot was performed to test the possibility of publication bias. A *p*-value of < 0.05 was considered statistically significant, and all analyses were performed using the Review Manager (Version 5.3; Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study characteristics

We identified 86 published studies between 1995 and 2019. After abstract scanning, 29 published studies were excluded because they did not investigate the association with HLA-DRB1, and 19 that failed to meet the inclusion criteria were also excluded as shown in Fig. 1. A total of 38 studies appeared to have met the inclusion criteria after the title and abstracts were thoroughly screened. The full-text of these articles were found and screened based on the inclusion criteria. After the full-text screening, we excluded two duplicated studies, one from the USA and one from China. Among the remaining studies, 15 were from Asians, nine from Caucasians, seven from Hispanic or Latin Americans, two from black sub-Saharan Africans, one from North-Africans in Tunisia, one from the Middle East in Iran and one from a mixed population in Canada. The characteristics of these studies are presented in Table S1.

3.2. Meta-analysis results

A total of 6645 cases and 9095 controls from 36 case-control studies were included in the current meta-analysis. There were 13 HLA-DRB1 family alleles and 44 specific alleles. Rare HLA-DRB1 alleles were defined as those reported in only one study and were subsequently excluded for further analysis in this meta-analysis. Among the 13 HLA-DRB1 family alleles investigated in this meta-analysis, DRB1*09 (OR = 1.30, 95% CI = 1.05 − 1.61) and DRB1*15 (OR = 1.60, 95% CI = 1.14 − 2.24) significantly increased the risk of cervical cancer, whereas DRB1*13 (OR = 0.66, 95% CI = 0.50 − 0.88) exerted a protective effect (Table 1).

A meta-analysis of HLA-DRB1 specific alleles and risk of cervical cancer is presented in Table 2. A total of ten specific alleles were associated with cervical cancer. The HLA-DRB1*04:01 (OR = 1.25, 95% CI = 1.09 − 1.43), DRB1*10:01 (OR = 1.45, 95% CI = 1.03 − 2.05), DRB1*11:01 (OR = 1.32, 95% CI = 1.05 − 1.65), DRB1*15:01 (OR = 1.21, 95% CI = 1.04 − 1.42) and DRB1*15:02 (OR = 1.55, 95% CI = 1.17 − 2.06) were associated with an increased risk of cervical cancer. In contrast, HLA-DRB1*04:06 (OR = 0.52, 95% CI = 0.35 − 0.77), DRB1*12:02 (OR = 0.61, 95% CI = 0.38 − 0.97), DRB1*13:01 (OR = 0.62, 95% CI = 0.52 − 0.74), DRB1*13:02 (OR = 0.57, 95% CI = 0.47 − 0.69) and DRB1*14:04 (OR = 0.37, 95% CI = 0.16 − 0.85) were associated with a decreased risk of cervical cancer. Forest plots and Funnel plots of these alleles are included as supplementary material in

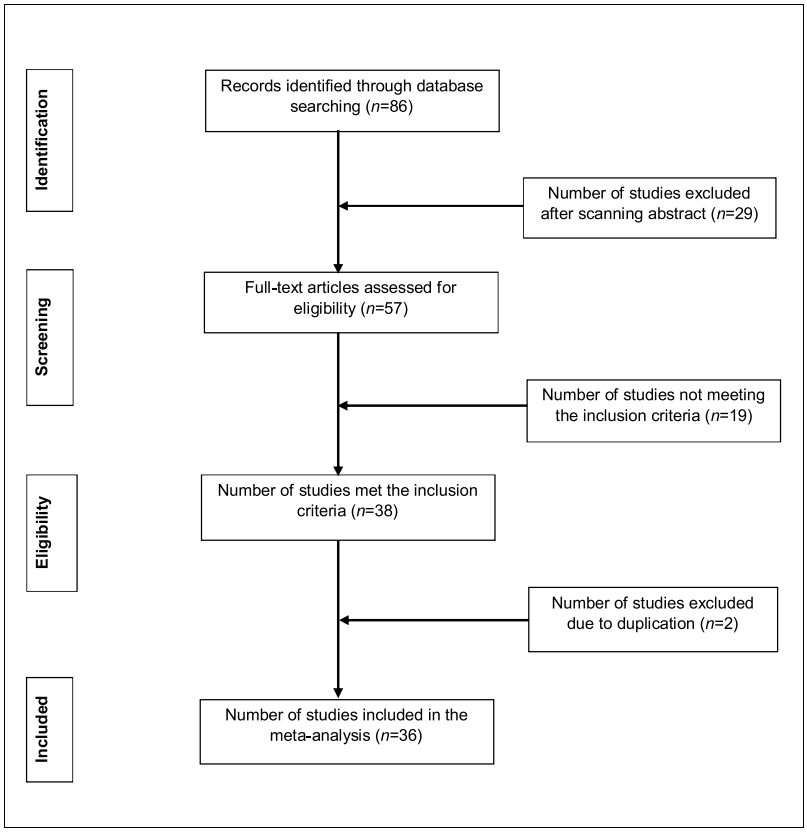

Fig. 1. Flowchart of study selection criteria.

Figs. S1 and S2, respectively.

3.3. Subgroup analysis

Since considerable heterogeneity existed among different studies from different ancestry populations, we therefore performed a stratified analysis according to the ethnicity of the study participants. The ethnic subgroups were categorised into Asians, Caucasians, Hispanic or Latin Americans, and black sub-Saharan Africans. In the Asian population, the HLA-DRB1*07:01 (OR = 1.41, 95% CI = 1.11–1.81), DRB1*09 (OR = 1.32, 95% CI = 1.05–1.67), and DRB1*15:02 (OR = 1.51, 95% CI = 1.09–2.10) were associated with an increased risk of cervical cancer (Table S2). However, HLA-DRB1*04:06 (OR = 0.52, 95% CI = 0.35 − 0.77), DRB1*12:02 (OR = 0.58, 95% CI = 0.36 − 0.94) and DRB1*13:02 (OR = 0.52, 95% CI = 0.31 − 0.86) were associated with a decreased risk of developing cervical cancer.

Subgroup analysis in Caucasians revealed that HLA-DRB1*04:01 (OR = 1.35, 95% CI = 1.05–1.74), DRB1*04:03 (OR = 2.37, 95% CI = 1.16–4.82), DRB1*11 (OR = 1.52, 95% CI = 1.12–2.06) and DRB1*15:01 (OR = 1.20, 95% CI = 1.05–1.37) were associated with an increased risk cervical cancer (Table S3). However, HLA-DRB1*13 (OR = 0.64, 95% CI = 0.46 − 0.88), DRB1*13:01 (OR = 0.58, 95% CI = 0.47 − 0.73), and DRB1*13:02 (OR = 0.64, 95% CI = 0.50 − 0.82) exerted a protective effect.

In the Hispanic or Latin American population, HLA-DRB1*15:01 (OR = 3.39, 95% CI = 1.74–6.63) and DRB1*15:03 (OR = 3.00, 95% CI = 1.30–6.94) increased the risk of cervical cancer, whereas DRB1*13 (OR = 0.53, 95% CI = 0.31 − 0.91) and DRB1*13:02 (OR = 0.29, 95% CI = 0.13 − 0.67) exerted a protective effect (Table S4). Subgroup analysis in the black sub-Saharan African ancestry population

Table 1
A meta-analysis of HLA-DRB1 family alleles and risk of cervical cancer.

Family alleles	No of studies	Cases	Controls	P_{het}	I^2 (%)	OR (95% CI)	*P*-value
01	14	200/2225	316/2806	0.47	0	0.88 (0.72 − 1.07)	0.19
03	12	318/2029	407/2357	0.002	62[a]	1.06 (0.80 − 1.41)	0.67
04	17	586/2462	803/3116	< 0.000001	74[a]	0.98 (0.75 − 1.29)	0.89
07	13	264/1973	332/2225	0.52	0	0.96 (0.81 − 1.15)	0.69
08	13	241/2004	331/2565	0.15	30	1.02 (0.84 − 1.23)	0.85
09	13	238/1906	240/2527	0.41	4	**1.30 (1.05 − 1.61)**	**0.01**
10	10	71/1740	75/1911	0.002	65[a]	1.22 (0.60 − 2.47)	0.58
11	15	320/2264	331/2918	0.0009	62[a]	1.31 (0.97 − 1.78)	0.08
12	10	186/1818	245/2091	0.21	25	0.85 (0.68 − 1.06)	0.14
13	16	312/2675	664/3745	0.0006	62[a]	**0.66 (0.50 − 0.88)**	**0.004**
14	14	224/2163	410/2787	0.14	30	0.87 (0.72 − 1.06)	0.17
15	15	550/2149	581/2808	< 0.00001	79[a]	**1.60 (1.14 − 2.24)**	**0.006**
16	12	119/1731	214/2389	0.93	0	0.86 (0.67 − 1.09)	0.21

P_{het} ; *P* value for heterogeneity, I^2 proportion of the total variation due to heterogeneity.
[a] Random-effect model was used when I^2 was > 50 % otherwise fixed-effect model was used.

Table 2
A meta-analysis of HLA-DRB1 specific alleles and risk of cervical cancer.

Specific alleles	No of studies	Cases	Controls	P_{het}	I^2 (%)	OR (95% CI)	*P*-value
01:01	13	383/2968	522/4047	0.05	42	0.92 (0.80 − 1.06)	0.26
01:02	07	37/900	71/1585	0.46	0	0.89 (0.59 − 1.35)	0.59
01:03	03	19/861	30/1266	0.21	37	1.22 (0.68 − 2.21)	0.50
02:02	02	16/186	18/243	0.03	78[a]	0.87 (0.15 − 4.95)	0.87
03:01	14	549/3106	801/4609	0.0001	68[a]	1.08 (0.83 − 1.39)	0.58
03:02	04	24/400	56/976	0.10	52[a]	0.89 (0.40 − 2.02)	0.79
04:01	11	513/2949	534/3914	0.06	43	**1.25 (1.09 − 1.43)**	**0.001**
04:02	06	25/1228	50/1802	0.83	0	0.78 (0.47 − 1.29)	0.33
04:03	07	61/1528	66/2239	0.15	37	1.44 (1.00 − 2.06)	0.05
04:04	09	215/2464	273/3411	0.79	0	1.02 (0.84 − 1.23)	0.86
04:05	09	174/1615	312/2744	0.74	0	0.90 (0.73 − 1.10)	0.31
04:06	04	34/967	119/1739	0.58	0	**0.52 (0.35 − 0.77)**	**0.001**
04:07	07	52/1493	74/2223	0.33	13	1.32 (0.89 − 1.96)	0.16
04:08	03	9/905	6/1105	0.74	0	2.10 (0.71 − 5.65)	0.19
04:10	04	36/967	43/1649	1.00	0	1.30 (0.82 − 2.05)	0.26
04:11	02	9/228	19/335	0.63	0	0.69 (0.31 − 1.55)	0.37
07:01	13	564/3157	681/4357	0.06	41	1.12 (0.99 − 1.27)	0.08
08:01	08	134/2384	172/3187	0.15	35	0.98 (0.78 − 1.25)	0.89
08:02	06	85/868	173/1658	0.59	0	0.94 (0.69 − 1.27)	0.67
08:03	05	80/1024	105/1681	0.85	0	1.23 (0.89 − 1.70)	0.21
08:04	04	9/886	19/1162	0.53	0	0.87 90.38 − 1.99)	0.74
09:01	10	131/1672	277/2708	0.03	51[a]	0.91 (0.62 − 1.34)	0.63
10:01	11	68/1726	86/2471	0.47	3	**1.45 (1.03 − 2.05)**	**0.04**
11:01	14	370/3409	429/4952	0.02	49	**1.32 (1.05 − 1.65)**	**0.02**
11:02	06	21/1115	52/1505	0.47	0	0.75 (0.44 − 1.27)	0.28
11:03	02	7/473	6/636	0.55	0	1.58 (0.53 − 4.71)	0.41
11:04	07	29/821	62/1487	0.59	0	0.72 (0.44 − 1.19)	0.20
12:01	09	51/1743	99/2534	0.48	0	0.74 (0.52 − 1.04)	0.09
12:02	03	28/550	88/1046	0.41	0	**0.61 (0.38 − 0.97)**	**0.04**
13:01	14	201/3106	420/4031	0.03	46	**0.62 (0.52 − 0.74)**	**< 0.00001**
13:02	12	155/2949	345/3999	0.65	0	**0.57 (0.47 − 0.69)**	**< 0.00001**
13:03	07	33/1230	42/1924	0.51	0	1.19 (0.75 − 1.88)	0.47
13:04	02	13/168	32/523	0.10	62[a]	1.22 (0.23 − 6.39)	0.82
14:01	14	134/2569	206/3742	0.58	0	1.01 (0.79 − 1.26)	0.99
14:02	04	44/431	156/1030	0.17	40	0.93 (0.44 − 1.95)	0.85
14:03	02	11/437	15/630	0.89	0	0.89 (0.40 − 1.98)	0.78
14:04	02	7/508	32/637	0.69	0	**0.37 (0.16 − 0.85)**	**0.02**
14:05	02	17/437	23/630	0.23	30	1.06 (0.55 − 2.05)	0.86
14:06	02	19/384	21/434	0.67	0	1.07 (0.56 − 2.04)	0.84
15:01	17	917/3921	1112/5780	0.01	49	**1.21 (1.04 − 1.42)**	**0.02**
15:02	07	124/1222	117/1941	0.92	0	**1.55 (1.17 − 2.06)**	**0.003**
15:03	04	33/348	33/648	0.04	63[a]	2.07 (0.65 − 6.61)	0.22
16:01	04	19/1018	33/1516	0.94	0	0.97 (0.54 − 1.74)	0.93
16:02	08	58/996	128/1891	0.08	45	0.97 (0.70 − 1.36)	0.87

P_{het} ; *P* value for heterogeneity, I^2 proportion of the total variation due to heterogeneity.
[a] Random-effect model was used when I^2 was > 50 % otherwise fixed-effect model was used.

revealed that the HLA-DRB1*09:01 (OR = 2.96, 95% CI = 1.24–7.07) allele increased the risk of cervical cancer, whereas HLA-DRB1*13:01 (OR = 0.23, 95% CI = 0.09 − 0.61) was associated with a decreased risk of cervical cancer (Table S5). Interestingly, our publication bias and sensitivity analysis revealed that our results are statistically robust as there was no obvious asymmetry from the Begg's funnel plots and change of overall pooled ORs, respectively Fig. S2.

4. Discussion

Our meta-analysis of 36 case-control studies provides evidence for the association of multiple HLA-DRB1 alleles with the risk of cervical cancer. Overall, HLA-DRB1*09, DRB1*15, DRB1*04:01, DRB1*10:01, DRB1*11:01, DRB1*15:01, and DRB1*15:02 alleles significantly increased the risk of cervical cancer, whereas DRB1*13, DRB1*04:06, DRB1*12:02, DRB1*13:01, DRB1*13:02 and DRB1*14:4 exerted a protective effect. By pooling data from different studies, a meta-analysis increases the statistical power of detecting a small genetic effect from individual studies with small sample sizes, and also reduces spurious associations associated with such studies to provide a more robust estimate of an effect.

HLA molecules are encoded by closely linked genetic loci which play a crucial role in the presentation of intracellular and extracellular antigens to immune cells. HLA class II molecules are particularly important as they present foreign antigen to $CD4^+$ T cells and elicit an immune response [53]. Genetic variation of HLA-DRB1 leads to structural changes in the peptide antigen-binding groove, which may increase or decrease the risk of pre-invasive cervical lesions and cervical cancer. Although the association between HLA-DRB1 alleles and cervical cancer has been observed in numerous studies, alleles found to be associated with cervical cancer have varied from study to study [22–24,40–42]. The observed differences may be due to differences in allele frequencies and local environmental risk factors among populations of different ancestry. In this study, HLA-DRB1*04:06, DRB1*07:01, DRB1*09, DRB1*12:02, DRB1*13.02 and DRB1*15:02 were associated with cervical cancer in Asians, whereas HLA-DRB1*04:01, DRB1*04:03, and DRB1*15:01 were associated with cervical cancer in Caucasians. In Hispanics or Latina Americans, HLA-DRB1*13:02, DRB1*15:01 and DRB1*15:03 were associated with cervical cancer. In the black sub-Saharan African population, HLA-DRB1*09:01 and DRB1*13:01 were associated with cervical cancer but these results are based on two available studies with small sample sizes [48,49]. Interestingly, prior reports have indicated that HLA-DRB1*04 alleles are associated with a decreased risk of cervical cancer in women

of Asian ancestry [23,31] and an increased risk of cervical cancer in women of Caucasian ancestry [34,36], consistent with our results. These findings suggest that HLA-DRB1 alleles may have different roles in populations of different ancestry.

Previous case-control studies have consistently reported that HLA-DRB1*15 alleles are associated with an increased risk of cervical cancer [23,28,37,42,47], whereas HLA-DRB1*13 alleles were associated with a decreased risk of cervical cancer [23,25,27,31,34], which are supported by our findings. In the current meta-analysis, women harbouring HLA-DRB1*15, DRB1*15:01, and DRB1*15:02 alleles had a 1.60, 1.21, and 1.55 fold increased risk of developing cervical cancer respectively, whereas in women with HLA-DRB1*13, DRB1*13:01, and DRB1*13:02 the risk of cervical cancer was decreased 0.66, 0.62, and 0.57 fold respectively. These findings suggest that HLA-DRB1*15 and their specific alleles may be important determinants of HPV-related cervical cancer progression, while HLA-DRB1*13 alleles may be important determinants of HPV-related cervical cancer regression and clearance, which is supported by the imputation of HLA class II alleles from a recent genome-wide study [54]. Moreover, our subgroup analysis by ancestry population revealed that HLA-DRB1*13 and DRB1*15 and their specific alleles are associated with cervical cancer in Asian, Caucasian and Hispanic or Latin American populations.

The main strengths of the present meta-analysis are that we included only high-quality case-control studies that investigated the association between HLA-DRB1 alleles and cervical cancer. Subgroup analysis allowed us to identify ancestry-specific alleles associated with cervical cancer in diverse populations. However, this study was limited by the small number of studies from sub-Saharan Africa, hence we were not able to perform an analysis of some HLA-DRB1 alleles. Moreover, we were not able to adjust for HPV subtypes and other covariates associated with cervical cancer since we did not have access to raw data from these studies. Nevertheless, our results are statistically robust as there was no evidence of any publication bias. In conclusion, our results provide strong evidence for the role of HLA-DRB1 alleles in the pathogenesis of cervical cancer in populations of diverse ancestry.

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CRediT authorship contribution statement

Abram Bunya Kamiza: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Steve Kamiza:** Methodology. **Christopher George Mathew:** Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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(http://www.mrc.ac.za/intramural-research-units/evolving-risk-factors-cancers-african-populations-erica-sa).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2020.101748.

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