

# Geographic distribution of cervical cancer-associated human leucocyte antigens and cervical cancer incidence in Finland

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**Summary:** Cervical cancer (CxCa) is a long-term sequelae caused by persistent human papillomavirus (HPV) infection. Genetic susceptibility to the persistent infection and CxCa is associated with certain human leucocyte antigen (HLA) types. The same susceptibility genes may also determine whether a woman will be protected against the persistent infection and against CxCa by HPV vaccination or not. A systematic review of literature identified following HLAs to be associated with CxCa: A11 (odds ratio [OR] = 1.4, 95% confidence interval [CI] 1.1–2.0); B7 (1.5, 1.1–2.0); B15 (0.6, 0.4–0.8); DR2 (1.2, 1.1–1.4) and DR6 (0.6, 0.5–0.8). In the Caucasian population, HLA-B7 and DR6, and DR2 and B15 antigens showed at least borderline associations. In view of a bone marrow donor registry at the Finnish Red Cross and the Finnish Cancer Registry, we created geographic distribution maps of index HLA frequencies and CxCa incidence in the fertile-aged Finnish population. Increased incidence of CxCa was found in a region of western coastal Finland, where frequency of two CxCa susceptibility genes (HLA-DR2 and B7) was increased, and frequency of one CxCa resistance gene (HLA-B15) was decreased. Whether or not HLA type determines also regional susceptibility to persistent HPV infection, and the success of HPV vaccination in preventing both the persistent infection and CxCa warrants further investigation.

**Keywords:** cervical cancer, human leucocyte antigen, human papillomavirus, geography, meta-analysis

## INTRODUCTION

Cervical cancer (CxCa) is the second most common cancer in women worldwide, with approximately half-a-million cases per year.<sup>1</sup> Developing countries bear most of the CxCa burden. Persistent infection with high-risk (hr) human papillomavirus (HPV, most notably types 16 and 18) is a prerequisite for the development of CxCa.<sup>2,3</sup> It is estimated that at least 50% of sexually active men and women will acquire hrHPV infections. Despite the substantial hrHPV infection rate, most of the cervical intra-epithelial neoplasia (CIN) spontaneously regress<sup>4</sup> and only up to 1% of the infections will progress to CxCa. Immunosuppressed individuals, e.g. transplant recipients or HIV-positive individuals, have an increased risk to develop CxCa and other HPV-associated cancers.<sup>5,6</sup> The

role of immunogenetics as a determinant of why some hrHPV infections progress to CxCa in immunocompetent individuals<sup>7</sup> is, however, open.

Significant differences in the frequency of various human leucocyte antigens (HLAs) in CxCa patients and controls, and downregulation of HLAs expressed on the CxCa cells *in vivo* have been reported.<sup>8</sup> With the modern DNA sequencing techniques, several HLA alleles associated with susceptibility or resistance to develop CxCa, such as HLA-A2402, HLA-B15, HLA-DRB1\*1501 (i.e. DR2) and HLA-DRB1\*13 (i.e. DR6), have been observed.<sup>9–12</sup>

HLA heterozygosity confers a favourable disease outcome for hepatitis B and HIV infections.<sup>13–15</sup> This suggests that individuals who carry different alleles in a particular major histocompatibility complex (MHC) gene may develop a more effective immune response against chronic viral infections. The heterozygote advantage has not been extensively explored either in the context of CxCa or in the HPV infection context. One published study, with cases from Costa Rica and the USA, did not show HLA class I related heterozygote advantage in CxCa.<sup>16</sup>

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Differences in the frequencies and penetration of HLA genes modulate the immune response both to persistent HPV infection and CxCa, and might cause variation in the incidence of CxCa by population/region. We performed a systematic review of HLA A, B and DR antigens associated with CxCa, and demonstrate the geographic distributions of the risk HLAs (overall and heterozygous) and CxCa incidence in Finland.

## MATERIALS AND METHODS

### Identification and eligibility of relevant studies

We made a literature search of PubMed database (from 1987 to September 2006) of all English language publications on the association between HLA and CxCa. The search strategy was based on combinations of the terms ('HLA' or 'human leucocyte antigen' or 'MHC') and ('cervix' or 'cervical') and ('cancer' or 'carcinoma' or 'neoplasia' or 'dysplasia' or 'CIN') and ('HPV' or 'human papillomavirus'). The inclusion criteria of the publications selected was all case-control studies with the endpoint CxCa (including squamous cell carcinoma (SCC) or carcinoma *in situ* (CIS) or CxCa), which had data on genetic susceptibility/resistance, i.e. HLA allele or antigen frequency in cases and controls for calculation of odds ratios (ORs) and 95% confidence interval (CI). Population structure (Caucasians and/or mixed descent included) was evaluated in stratified analysis. HPV status and Hardy-Weinberg equilibrium (HWE) in the control group were not taken into account.

Weighted mean ORs with 95% CI were calculated only for those HLA alleles and antigens, which had been significantly associated with CxCa at least in one of the selected publications, to have a prior hypothesis to avoid too much *post hoc* data exploration. The calculation was done according to a fixed-effects model (Mantel-Haenszel method), and was performed using the statistical program R version 2.0 (R Development Core Team). Woolf's test for heterogeneity was evaluated. When statistically significant heterogeneity ( $P$  value  $<0.1$ ) was found, we included the results from the random-effects model (DerSimonian-Laird method).

### Finnish Bone Marrow Donor Registry

The Finnish Bone Marrow Donor Registry (FBMDR) was established in 1992 by the Finnish Red Cross to facilitate bone marrow transplantations in Finland.<sup>17</sup> Currently, the Registry has approximately 20,000 donors with an average age of 32.6 years (range 18-45 years) and 64% of the donors are women. All the donors have been HLA typed for the A, B and DR antigens using serologic or genomic methods. To make comparisons of HLA alleles more feasible, all genomic results were converted into their serological broad specificities, e.g. DRB1\*15 and DRB1\*16 were marked as DR2.

The HLA frequency rate was obtained from a total of 19,475 donors that contributed with 38,950 sets of HLA allotypes for each of the HLA types (DR, A and B), and resulted in the coverage of 441 out of 448 communities in

Finland (Figure 1). HLA frequency for the communities was calculated as HLA-allotype frequency in a given community/total of blood donors tested in the same community. HLA heterozygosity frequency rates were calculated similarly.

### Finnish Cancer Registry and mass screening for CxCa

The Finnish Cancer Registry is population based and countrywide. It receives notifications from hospitals and physicians, from cytology and pathology laboratories, and also utilizes death certificate information. The coverage is almost 100%.<sup>18</sup> The Finnish mass Pap smear programme to screen precancerous lesions of the cervix uteri was initiated in 1963 by the Finnish Cancer Society. Screening is free of charge and, in most municipalities, offered to women between 30 and 60 years of age. The screening interval is normally five years, and the mean attendance rate is 70%.<sup>19</sup>

### Mapping method

We calculated the HLA frequency rates for each community. We also calculated truncated age-adjusted (world standard population) CxCa incidence rates for age range 15-34 years during 1965-2004.

Spatial variation in the HLA prevalence rates and CxCa incidence rates were visualized by a series of maps. The rates for biggest cities ( $>35,000$  inhabitants) were shown as coloured circles (size indicating population of the city), while the remaining observations were smoothed to  $2 \times 2$  km<sup>2</sup> grids. The rate of each map/pixel was calculated as weighted average of rates in communities within 250 km from the middle of grid. The young (15-34 year old) population was a direct weighting coefficient, whereas distance was used for inverse weighting. Areas with less than one inhabitant per square kilometre were masked.

## RESULTS

### Systematic review and meta-analysis

Out of a total of 225 publications found from PubMed, 67 publications were eligible for further analysis by abstract fulfilling the selection criteria. Since the HLA data in the FBMDR are available only for HLA A, B and DR antigens, altogether 17 pertinent publications (seven considering HLA A or B, and 13 considering DRB1) were selected for the final meta-analysis (Table 1). Excluded publications contained information about HLA DQ alleles, HLA haplotype or the outcome was not CxCa.

In the meta-analysis, we used a combined approach including both the frequencies of a given HLA or of a corresponding HLA allele family (broad specificity) or weighted frequencies of specific alleles belonging to the family. When several HLA alleles were included for a specific HLA allele family, we excluded studies that evaluated only one allele from the combined analysis of a given HLA, but included all those studies that reported frequencies of HLA allele family. Different numbers of

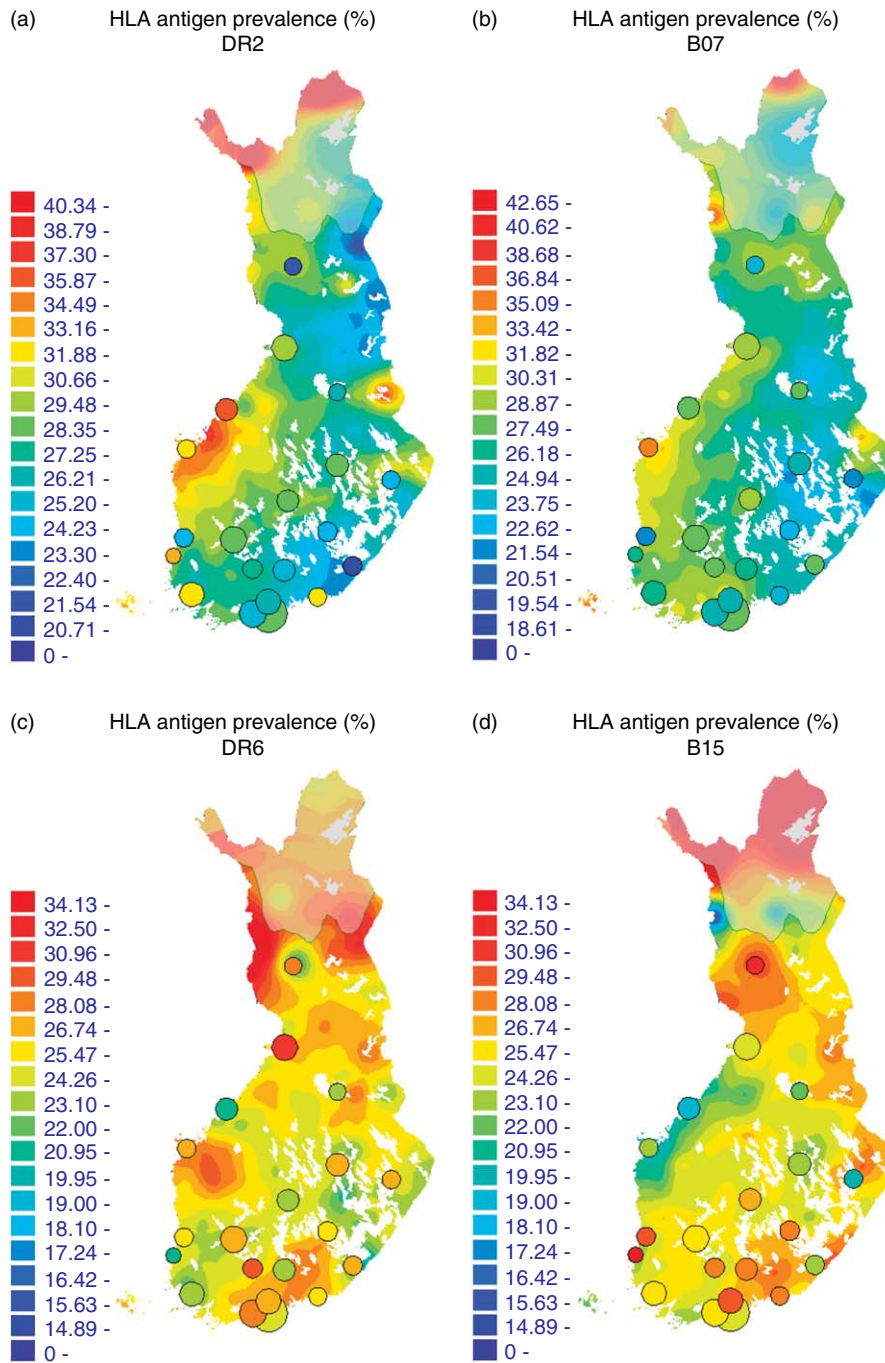


Figure 1 HLA frequencies in young Finnish population. Map generated from sample sizes of 19,475 donors from the FBMDR during 1992-2004. The biggest cities are circled with the size of the circle indicating the size of the city

alleles (1-5, i.e. 1 allele for DR3 and 5 for DR2) were included for specific HLAs. The test of heterogeneity revealed that most of the meta-analyses were heterogeneous when the study of Krul *et al.*<sup>25</sup> was included (data not shown). Following exclusion of this study as an outlier, results with the fixed-effect model were available for almost all HLAs (Table 2).

We found three HLAs to be associated with susceptibility to CxCa (significantly increased ORs for A11, B7 and DR2), and two HLAs that conferred a protective effect (significantly decreased ORs for B15 and DR6) (Table 2).

Next, the meta-analysis was done solely among Caucasian population to make the results coherent with the Finnish population-based data on HLA and CxCa

Table 1 Characteristics of studies included in meta-analysis

Study	Year	Ethnicity	Subject numbers		Approach for HLA typing
			Control	Cases	
Glew <i>et al.</i> <sup>20</sup>	1993	American	504	58	Serotyping (DR, A and B)
Duggan-Keen <i>et al.</i> <sup>21</sup>	1996	British	144	129	Genotyping (DR), serotyping (A and B)
Allen <i>et al.</i> <sup>22</sup>	1996	Swedish	350	300	Genotyping (DR)
Sastre-Garau <i>et al.</i> <sup>23</sup>	1996	French	165	126	Genotyping (DR)
Montoya <i>et al.</i> <sup>24</sup>	1998	Spanish	138	142	Serotyping (A)
Krul <i>et al.</i> <sup>25</sup>	1999	Dutch	1133	169	Serotyping (DR, A and B)
Maciag <i>et al.</i> <sup>26</sup>	2000	Brazilian	257	161	Genotyping (DR)
Cuzick <i>et al.</i> <sup>27</sup>	2000	British	155	116	Genotyping (DR)
Lin <i>et al.</i> <sup>28</sup>	2001	Senegalese	190	55	Genotyping (DR)
Beskow <i>et al.</i> <sup>11</sup>	2001	Swedish	469	433	Genotyping (DR)
Madeleine <i>et al.</i> <sup>12</sup>	2002	American	381	315	Genotyping (DR)
Dehaghani <i>et al.</i> <sup>29</sup>	2002	Iranian	36	23	Genotyping (DR)
Matsumoto <i>et al.</i> <sup>30</sup>	2003	Japanese	138	57	Genotyping (DR)
Zehbe <i>et al.</i> <sup>31</sup>	2003	Swedish	300	27	Serotyping (A and B)
Chan <i>et al.</i> <sup>9</sup>	2005	Chinese	572	108	Genotyping (A)
Yang <i>et al.</i> <sup>8</sup>	2006	Chinese	578	252	Genotyping (DR)
Chan <i>et al.</i> <sup>10</sup>	2006	Chinese	258	111	Genotyping (B)

Table 2 Meta-analysis on the association between HLAs (A, B and DR) and cervical cancer in all population and by Caucasian ethnicity

Population										
Antigens*	All					Caucasians				
	Studies	Control/cases	OR <sup>†</sup>	95% CI		Studies	Control/cases	OR <sup>†</sup>	95% CI	
DR2	10	3421/1779	<b>1.3</b>	<b>1.1</b>	<b>1.5</b>	5	2222/1231	<b>1.1</b> <sup>§</sup>	<b>1.0</b> <sup>‡</sup>	<b>1.4</b>
DR3	11	3582/1967	1.0	0.8	1.1	7	2521/1476	1.0 <sup>§</sup>	0.8	1.3
DR4	8	2659/1544	1.1	1.0	1.3	6	2366/1360	1.1	1.0	1.3
DR6	6	2309/1137	<b>0.6</b> <sup>§</sup>	<b>0.5</b>	<b>0.8</b>	4	1862/921	<b>0.7</b>	<b>0.5</b>	<b>0.8</b>
DR7	12	3720/2024	1.2 <sup>§</sup>	0.9	1.5	7	2521/1476	1.1	0.9	1.3
DR9**	12	4698/2077	1.1	0.9	1.4	7	3499/1529	0.9	0.5	1.5
DR10**	12	4698/2077	1.5	1.0	2.2	7	3499/1529	<b>2.4</b>	<b>1.3</b>	<b>4.4</b>
DR11	9	2554/1712	1.1	0.9	1.4	4	1355/1164	1.2	1.0	1.6
A2	5	2460/485	0.9 <sup>§</sup>	0.4	1.9	5	2125/464	1.2 <sup>§</sup>	0.8	2.0
A11	4	2322/343	<b>1.4</b> <sup>§</sup>	<b>1.1</b>	<b>1.9</b>	3	1750/235	1.1	0.7	1.7
A24	4	2322/343	0.5 <sup>§</sup>	0.2	1.6	3	1750/235	1.1	0.7	1.6
B07	4	2008/346	<b>1.5</b>	<b>1.1</b>	<b>2.0</b>	3	1750/235	<b>1.5</b>	<b>1.1</b> <sup>‡</sup>	<b>2.0</b>
B15	4	2008/319	<b>0.6</b>	<b>0.4</b>	<b>0.8</b>	3	1750/208	<b>0.7</b>	<b>0.4</b>	<b>1.1</b> <sup>‡</sup>
B44	4	2008/346	1.3	1.0	1.8	3	1750/235	1.4	1.0	1.8
B51	3	1504/288	1.5	0.9	2.4	2	1246/177	2.0	1.0	3.8
B57	4	2002/346	1.3	0.6	2.6	3	1750/235	1.3	0.7	2.8

\*All alleles of an HLA allele family corresponding to an HLA were weighted with a given study and combined for the meta-analysis

<sup>†</sup>Fixed-effect estimates

<sup>‡</sup>The confidence limit is above 1.0 but below 1.1

<sup>§</sup>Random-effect model presented

\*\*Estimates from the fixed model including the study of Krul *et al.*<sup>20</sup>

incidence. The HLA DR2 and B15 associations appeared to lose statistical significance (Table 2), but HLA B7 and DR6 antigens, and in addition, DR10, proved to be associated with a significantly increased or decreased risk of CxCa (Table 2). For HLA DR2, DR4, DR11, B15 and B44 associations of borderline significance (including confidence limit <1.1) were noted in the Caucasian population. When specific alleles of allele families were evaluated, two alleles (DRB1\*1301 and DRB1\*1302), both included in DR6 broad specificity, conferred protection against CxCa (OR=0.55, 95% CI 0.4-0.7 and OR=0.6, 95% CI 0.4-0.8,

respectively), and one specific allele (DRB1\*1501), which is included in DR2 broad specificity, showed significant or borderline significant associations with susceptibility to CxCa (OR=1.2, 95% CI 1.0-1.5).

### HLA distributions in the young Finnish population

The HLA A, B and DR allotypes were obtained from the total of FBM donors screened ( $n=19,467$ ,  $n=19,458$  and  $n=18,808$ , respectively). Considerable variation in the

distribution of all HLAs was observed in several regions in Finland. The total number of allotypes, allotype frequencies inside the antigen family and antigen population frequencies were: for HLA-DR2 (5386, 14.3% and 28.6%), for B7 (5358, 13.8% and 27.5%), for DR6 (4867, 12.9% and 25.9%), for B15 (5014, 12.9% and 25.8%) and for DR10 (352, 0.9% and 1.9%), respectively.

On the basis of the results of the meta-analysis, we decided to make maps for the following HLAs: DR2 (including DRB1\*15), DR6 (including DRB1\*13), DR10, B7 and B15, which showed constantly significant association with CxCa and/or particularly high- or low-risk estimates of CxCa for the Caucasians.

Frequencies described in the maps for HLA-DR2 and B7, and to a lesser extent HLA-DR10 (data not shown), antigens showed strong clustering on the western coast of Finland around the city of Vaasa (Figure 1). The HLA-DR2 and B7 frequencies were diluted in the rest of the country with the lowest prevalence in the southeastern regions of the country. HLA-DR6 appeared to be clustered in the same region as DR2 and B7 albeit somewhat inland around the city of Seinäjoki. HLA-B15 frequency map showed a relative lack of the antigen again on the middle west coast areas (Figure 1).

### Spatial variation of CxCa incidences in young Finnish women population

Clear spatio-temporal variation over the last 40 years was observed for CxCa incidence among young (15–34 year old) women in Finland (Figure 2). In the 1960s, the incidences of CxCa varied between 1 and 4/100,000 women years by region, but almost all over Finland the incidences decreased to 1/100,000 considerably following the full implementation of screening for CxCa in the late 1960s. Since 1995, the incidence has again raised up to four cases/100,000 women in the south west of Finland. However, a region of communities localized in the middle west coast of Finland, around the city of Vaasa, showed persistently increased incidence of CxCa during three decades (1975–2004). This was also true for women aged 15–39 years (data not shown). Comparable incidences were noted only in the cities of Espoo and Vantaa (between 1995 and 2004) in the Helsinki metropolitan area.

Possible heterozygote advantage was explored by comparing population frequencies of the two HLA-susceptibility antigens (DR6 and B15) for three pairs of similar sized cities (Espoo or Vantaa versus Tampere and Vaasa versus Seinäjoki) with increased or decreased CxCa incidence, respectively (Figure 2d, Table 3). Comparable, relatively homogeneous heterozygosity frequencies (20–27%) in the young populations of the selected cities, also participating in population-based HPV vaccination trials, were observed.

### DISCUSSION

Familial risk of CxCa has been established.<sup>32–36</sup> It may be explained in part by socioeconomic and behavioural variables, such as split families and risk-taking behaviour,<sup>37</sup>

but also by HLA-associated immunogenetic factors. Here, we illustrate a possibility to identify clusters in the Finnish population that display similar geographic distribution of specific HLAs and CxCa incidence.

We found in our meta-analysis a statistically significant association between CxCa and HLA-A11, B7, B15, DR2 and DR6. For the Caucasian populations, HLA-B7, DR6 and DR10, and also DR2 for one allele, were found to be significantly associated with CxCa. The HLA-DRB1 alleles included in the meta-analysis had a strong weight on their point estimates, but our results are in line with previous studies where DRB1\*15 and DRB1\*13 allele families (DR2 and DR6 broad specificities) have been firmly associated with CxCa (for a systematic review see Yang *et al.*<sup>8</sup>). We acknowledge the possible bias associated with the weighted mean approach used, however, the main objective of our meta-analysis was to obtain *a priori* estimates to allow development of all possibly relevant CxCa-associated HLA maps of Finland.

The meta-analysis resulted in somewhat vague observations for the alleles of HLA A and B antigens. The applied combination approach may have been useful above, but could not be used here because of low number of studies. Low number of observations and borderline significances were noted, especially among analyses restricted to the Caucasians. Thus, we decided to include both HLA-B7, which showed significant susceptibility to CxCa both in the mixed and the Caucasian populations, and HLA-B15, which showed strong protection only in the mixed population, in the maps.

HLA-type distributions across Finland were first studied 10 years ago by Siren *et al.*,<sup>17</sup> who also used data of the FBMDR. They reported regional differences in several of the HLAs, such as A9, B7, B15, B12 and DR3. However, the authors described mostly those HLAs that participate in the transplantation/rejection process. Our maps confirm the previously reported regional distributions of the HLA-B7 and B15 antigens. The latter localized mainly in the southwestern parts was, however, lacking from the middle west coast of the country.<sup>15</sup> The geographical distributions of the DR2, DR6 and DR10 have not been described before for Finland. We understand that the HLA distributions from the FBMDR may, in part, differ from the general population due to the healthy worker factors, such as increased health consciousness or urban living, which might introduce different CxCa screening compliance rates. However, to consider differences in the implementation of the screening programme by communities, we used CxCa incidence rates truncated to age 15–34 years. By allowing only one screening round (at the age of 30) outside the Helsinki metropolitan area, this controlled for all the possible confounding by screening effects in the other parts of the country.

The area of middle west coast of Finland (around the city of Vaasa) displayed one of the highest incidences of CxCa, and high frequencies of HLA-DR2 and B7 antigens and also a relatively high frequency of DR10 antigen (data not shown). In the same area, low frequency of HLA B15 was noted. A low frequency of HLA DR6 was also observed, but more inland (around the city of Seinäjoki). Thus, 2/2

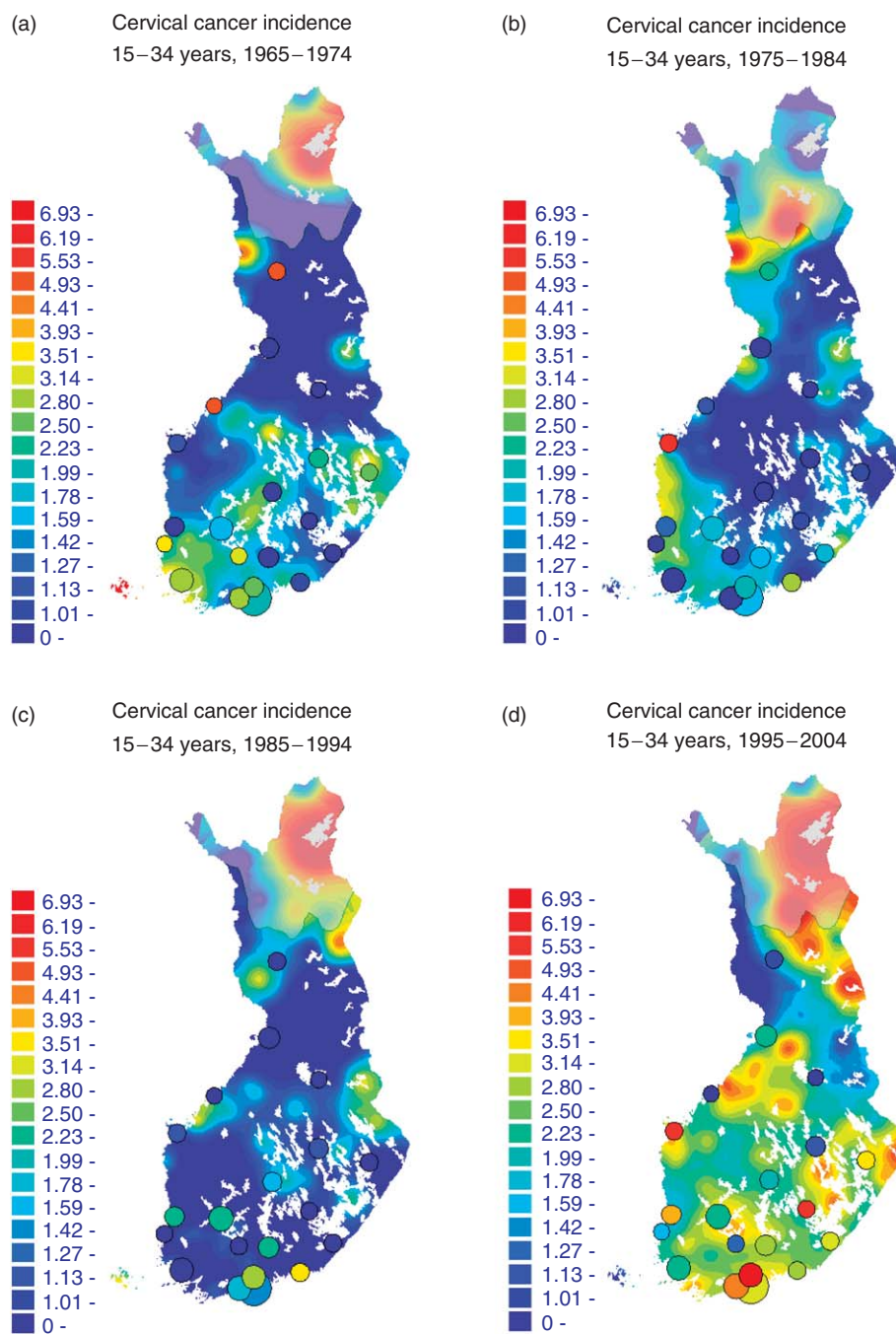


Figure 2 CxCa incidence in 15- to 34-year-old Finnish women during the periods of 1965–1974, 1975–1984, 1985–1994 and 1995–2004, respectively. Incidence rates/100,000. The biggest cities are circled with the size of the circle indicating the size of the city

(or 3/3) genetic susceptibility factors for CxCa, and a relative absence of one of the two resistance factors of CxCa clustered with CxCa incidence in the Vaasa area. Thus, specific frequencies of HLAs might explain, in part, the locale-specific high incidence of CxCa. It should be noted that the middle west coast of Finland is heavily inhabited by Swedish-speaking minority of the Finnish population originating from Sweden, which probably gives rise to the

observed differences in the HLA-type distributions between the Vaasa area and inland.

The heterozygosity of HLA-B15 and DR6 antigens was almost evenly distributed in cities with low or high CxCa incidence (Table 3). This suggests no marked heterozygote advantage for the inland population having lower CxCa incidence with regard to the two putative CxCa resistance genes. This differs from the observations made with regard



Table 3 Frequency of heterozygosity and heterozygosity proportion of HLA types conferring resistance to CxCa in selected HPV vaccination study sites with low or high incidence of CxCa among 15- to 34-year-old women\*

Study site	Absolute number of heterozygous		Heterozygosity frequency		Heterozygosity proportion	
	B15	DR6	B15	DR6	B15	DR6
Seinäjoki <sup>†</sup>	36	34	25.7	25.8	94.7	94.4
Vaasa <sup>‡</sup>	43	47	22.5	23.4	93.5	92.2
Vantaa <sup>‡</sup>	205	183	20.8	23.2	94.5	94.3
Espoo <sup>‡</sup>	225	225	26.9	24.6	93.4	90.4
Tampere <sup>‡</sup>	203	203	22.6	23.2	93.1	92.3

\*Frequencies based on the total of HLA family antigens and proportions obtained from the total of the specific HLA type

<sup>†</sup>HPV vaccination study sites where low CxCa incidences in young Finnish female population were observed

<sup>‡</sup>HPV vaccination study sites with high CxCa incidences observed

to persistent hepatitis B virus or HIV infections.<sup>13,15,38</sup> Hence, HLA heterozygosity may not need to be considered when comparing the HPV vaccination study sites.<sup>39</sup>

Some HLA genes might be in linkage disequilibrium with other non-HLA-related genes, which could be a confounder here. The possibility of chance observations in the HLA frequency data, and especially in CxCa incidence maps of the young adults is high. There also exist differences in the implementation of the screening programme by communities.<sup>19</sup> This may, however, not explain the observed CxCa clusters in women under 35 years of age as only up to 60% of them were screened once.

In addition to CxCa, HLAs have also been associated with susceptibility to persistent hrHPV infections.<sup>40</sup> A silent HPV16 epidemic started already in the 1980s in Finland due to general increase in the sexual risk-taking behaviour in the young after early 1970s.<sup>41-43</sup> HPV16 seroprevalence has increased, especially in the southernmost part of Finland, but it was also noted in the city of Vaasa among the adolescent and young (<23 years of age) women during 1988-1994<sup>43</sup> and is a prerequisite for the high CxCa incidence in the Vaasa region during 1995-2004, in young adult women (<35 years of age). The increase in HPV16 seroprevalence is, however, almost uniform all over southwestern Finland, and does not provide sufficient explanation for the observed CxCa cluster. Ecological analysis of geographical distributions of HPV infections (exposure), HLAs (susceptibility) and CxCa incidence (endpoint) are now warranted, and should be followed by individual-level cohort studies to confirm the role of HLA in CxCa.

In conclusion, geographic overlap of two susceptibility genes (HLA-DR2 and B7) and missing of one resistance gene (HLA-B15) with increased incidence of CxCa was found. The possibility that HLA type and associated genes cluster with high incidence of persistent hrHPV infections, and also determine the success of preventing both the persistent infections and CxCa by HPV vaccination warrants further investigation.

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