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Biomolecular and epidemiological aspects of human papillomavirus induced cervical carcinogenesis

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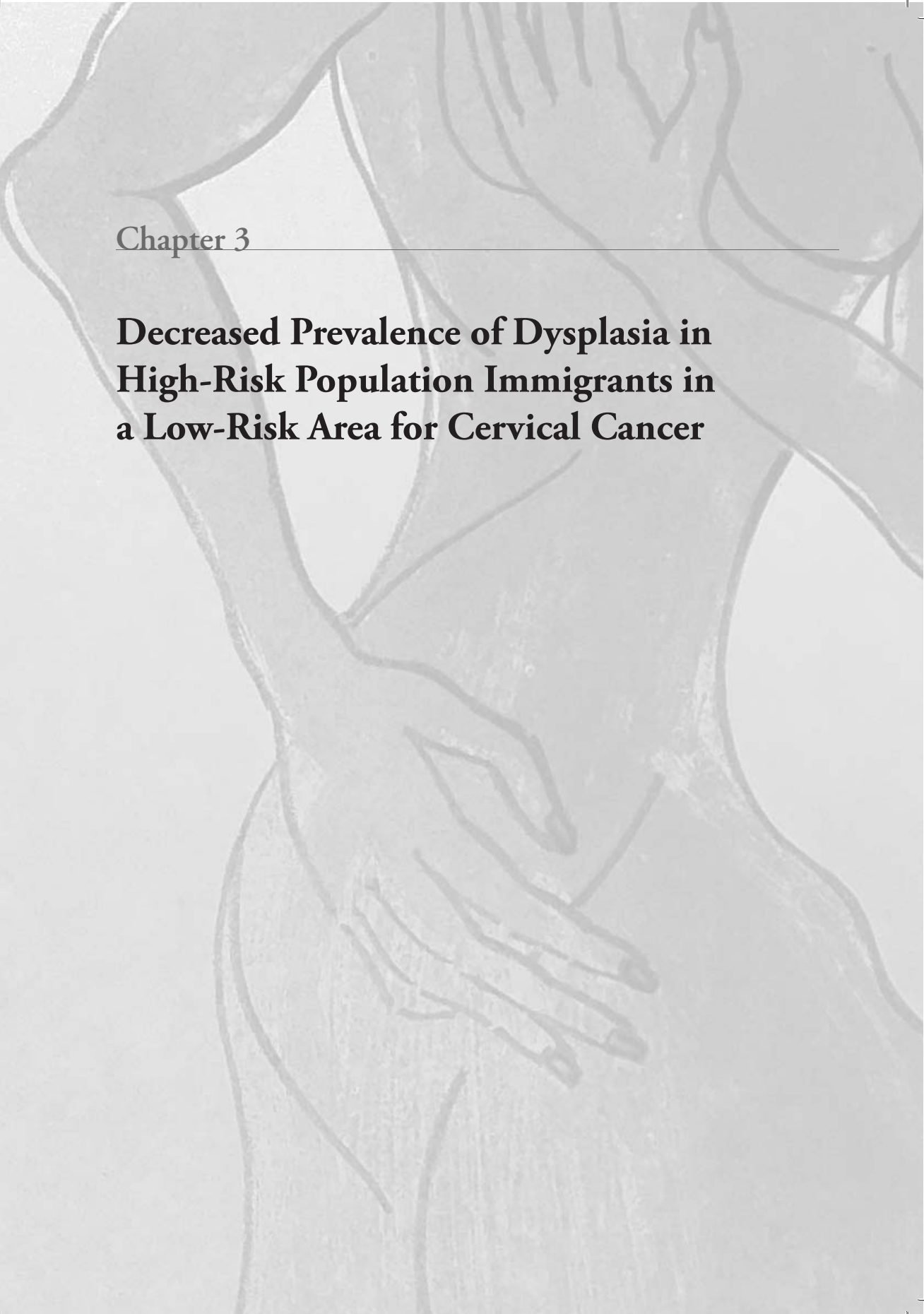
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Chapter 3

Decreased Prevalence of Dysplasia in High-Risk Population Immigrants in a Low-Risk Area for Cervical Cancer

Abstract

Incidence rates of cervical cancer and its precursors vary considerably, with the highest rates found in developing countries. Differences are influenced by endogenous and exogenous factors. Comparing cytological abnormality incidence rates from a high-risk population in the original high-risk area with those of women from this high-risk population who have immigrated to a low-risk area could give insight in the significance of endogenous versus environmental factors. Smears collected from Surinamese women attending the Surinamese screening programme and smears collected from immigrant Surinamese women attending the Dutch screening programme were cytologically analysed using the Dutch microscopical coding system KOPAC. Statistical analysis was performed by using logistic regression to calculate (age-adjusted) odds ratios. The age-adjusted odds ratios of having dysplasia were higher for Surinamese women living in Suriname versus Surinamese immigrant women and increased with increasing P-scores: 0.77 (0.31-1.91) for borderline changes, 1.62 (0.58-4.57) for mild dysplasia and 3.20 (1.55-6.60) for moderate to severe dysplasia/neoplasia. We conclude that fewer cases with dysplasia are present in a high-risk population that has immigrated to a low-risk area for cervical cancer than in the high-risk population continuously living in a high-risk area. This finding emphasises the importance of environmental factors.

Introduction

Cervical carcinoma remains the second most common cancer among women worldwide, with over 470,000 new cases diagnosed yearly¹. Incidence rates of cervical cancer and premalignant cervical lesions vary considerably and the highest incidence rates are found in developing countries¹⁻³. The differences in incidence rates are influenced by exogenous and endogenous factors⁴. Important exogenous or environmental factors are human papillomavirus (HPV, the unifying risk factor for cervical cancer^{5,6} and its precursors⁷), screening history and sexual lifestyle^{4,8}. Endogenous factors consist of immunogenetic characteristics among others. Although these risk factors have been studied previously, the relative influence of endogenous and environmental factors on the differences in incidence rates between high- and low-risk areas remains unclear. It is possible to obtain insight in this matter by comparing the cytological abnormality incidence rates of immigrants from a high-risk area for cervical cancer with those of the source population.

Suriname is a high-risk area for cervical carcinoma with an incidence of at least 26.7 per 100,000 women and a three- to sixfold higher percentage of the advanced FIGO stages (IIB-IV) than found in low-risk areas⁹. Almost half of the Surinamese population lives in the Netherlands, as a result of Suriname being a former Dutch colony. The demographics of the Surinamese immigrants in the Netherlands and the source population in Suriname are similar^{10,11}, which provides us with a unique opportunity for research. The purpose of this study was to compare cervical cytological abnormality incidence rates in a high-risk population living in a high-risk area for cervical cancer and the incidence rates in members of the same high-risk population who have emigrated and are living in a low-risk area.

Material and Methods

Surinamese Study Population from the Surinamese Screening Programme

In Suriname the nationwide screening programme started as part of the bilateral medical care programme between Suriname and the Netherlands. It targets women aged between 20 and 55. For most Surinamese women this is their first smear taken ever, as this is the first screening programme implemented in Suriname. All smears are analysed by the Cytology Department of the Lobi Foundation and by the Department of Pathology, Academic Hospital, Paramaribo, Suriname. The response rate of the targeted women of the Surinamese screening programme in this period was estimated at 50%. Between 1997 and 2001 a random sample of the smears (n = 890, stratified by race) was also analysed by the Department of Pathology, Leiden University Medical Centre, Leiden, the Netherlands. For this study, the smears analysed in the Netherlands were used. Only smears from ethnic

groups who have immigrated to the Netherlands were included in the study population. The final number of smears from Suriname in this study was 686.

Surinamese Study Population from the Dutch Screening Programme

The regular Dutch screening programme targets women in the Netherlands between 30 and 60 years of age. Among these women are Dutch citizens and legal immigrants. The smears of all women attending the screening programme in the Western region of the Netherlands between 1997 and 2001 were collected. From these smears, those of women born in Suriname were selected, and numbered 7613 in total. All immigrant Surinamese women in this study are, therefore, first-generation immigrants. The smears used in this study were the first smears taken of these women. The Surinamese immigrants are from all social levels of the Surinamese population¹⁰ and are comparable with the source population in terms of socio-economic status and demographic characteristics¹¹. The response rate of immigrant Surinamese women in this period was 58% (Dr M.E. Boon, SBBW, the Netherlands).

Cervical Smearing

The majority of the smears in Suriname were taken in one of the mobile medical units or at a medical clinic in Paramaribo. A smear sample was taken and spread on two glass slides, fixed and stored at room temperature until use. For every woman a new, disposable cervix brush was used. One glass slide was included in the Surinamese screening programme, the other was shipped to Leiden, the Netherlands for review. The smears in the Dutch screening programme were mostly taken at general physician practices throughout the western region of the Netherlands.

Cytological Diagnosis with KOPAC

The smears from Suriname were shipped from Suriname to Leiden. On all Surinamese smears, both from the Surinamese and the Dutch screening programme, standard Papanicolaou staining was performed for diagnostic purposes. The smears were reviewed by different laboratories in the western part of the Netherlands using the same protocol for cytological analysis. Cytological findings were coded using the KOPAC system, since the 1980s the official Dutch microscopical coding system for cytological analysis of cervical smears. Studies comparing different laboratories using the KOPAC system revealed no significant inter-laboratory differences in cytological scores (data not shown).

Smears are given a P-score for normal squamous epithelium (P1), borderline changes (P2-3) and (pre)neoplastic changes in the squamous epithelial cells, varying from P4 (mild dysplasia) to P9 (invasive squamous cell carcinoma) (**TABLE 1**). Inflammation is coded with "O" and consists of different codes for the variety of inflammation types. Koilocytosis, a cavity around the nucleus, was coded as "O1" for cells with and without abnormalities.

TABLE 1

KOPAC, the official Dutch microscopical coding system for cytological analysis of cervical smears. Description and translation of codes for normal squamous epithelial cells and (pre)neoplastic changes, the "P-codes"

KOPAC Code	Description	Bethesda
P1	Normal	Normal
P2-3	Borderline Changes	ASCUS
P4	Mild Dysplasia	(L)SIL
P5	Moderate Dysplasia	(H)SIL
P6	Severe Dysplasia	(H)SIL
P7	Carcinoma in Situ	(H)SIL
P8	Micro invasive Carcinoma	Carcinoma
P9	Squamous Cell Carcinoma	Carcinoma

Statistical Analysis

Odds ratios (OR) and age-adjusted ORs with 95% confidence intervals (CIs) of the (pre)neoplasia P-scores were calculated for the Surinamese screening population from Suriname versus the immigrant Surinamese screening population from the Netherlands by using logistic regression. The smears scored P1 (normal squamous epithelial cells) were used as a reference group.

Results

The median age for Surinamese women attending the Surinamese screening programme (SuS) was 34 (mean 35.5) years and the range was 14 to 75. For immigrant Surinamese women attending the Dutch screening programme (SuN), the median age was 40 (mean 41) years with a range of 30 to 63. This difference is due to the fact that the screening programme in Suriname starts at an earlier age (20) than does the programme in the Netherlands (30).

Smears were unsuitable for cytological analysis in 46/686 (6.7%) of the SuS and in 73/7613 (1.0%) of the SuN. The observed prevalence of (pre)neoplastic changes in the SuS was higher for mild (P4) and moderate to severe dysplasia/neoplasia (P5-9) compared to the SuN (**TABLE 2**).

The age-adjusted odds ratios for SuS versus SuN increased with increasing P-scores up to OR = 3.2 (CI 1.55-6.60) for P5-9. The odds ratios and the age-adjusted odds ratios of the different (pre)neoplastic stages are shown in **TABLE 2**.

The abnormal smear prevalence (P≠1) per age group among the SuS was 7/196 (3.6%) for < 30, 12/248 (4.8%) for 30-39, 3/123 (2.4%) for 40-49 and 3/73 (4.1%) for ≥ 50 years.

TABLE 2

P-Scores, odds ratios and age-adjusted odds ratios of (pre)neoplastic changes (P2-9) for Surinamese women living in Suriname

(Pre) neoplastic changes	SuS ¹ (n = 640) N (%)	SuN ² (n = 7540) N (%)	OR ³ _{crude}	95% CI ⁴ _{crude}	OR ⁵ _{adj}	95% CI ⁵ _{adj}
P1	615 (96.1)	7340 (97.4)	1.00	reference	1.00	reference
P2-3	6 (0.9)	111 (1.5)	0.65	0.28-1.47	0.77	0.31-1.91
P4	9 (1.4)	40 (0.5)	2.69	1.30-5.56	1.62	0.58-4.57
P5-9	10 (1.6)	49 (0.6)	2.44	1.23-4.83	3.20	1.55-6.60

¹Smears from Surinamese women living in Suriname

²Smears from Surinamese women living in the Netherlands

³Odds Ratio

⁴Confidence Interval

⁵Adjusted for age groups

TABLE 3

Correlation of normal squamous epithelial cells (P1) and (pre)neoplastic changes (P2-9) with koilocytosis (O1)

(Pre) neoplastic changes	No. SuS ¹ O1 N (%)	No. SuN ² O1 N (%)
P1	1/615 (0.2)	1/7340 (0)
P2-3	2/6 (33.3)	13/111 (11.7)
P4	8/9 (88.9)	3/40 (7.5)
P5-9	7/10 (70.0)	1/49 (2.0)
All	18/640 (2.8)	18/7540 (0.2)

¹SuS = Smears from Surinamese women living in Suriname

²SuN = Smears from Surinamese women living in the Netherlands

For the SuN it was 86/3011 (2.9%) for 30-39, 89/3155 (2.8%) for 40-49 and 25/1374 (1.8%) for ≥ 50 years.

Adjusting odds ratios after exclusion of the SuS aged < 30 did not alter our results.

Koilocytosis occurred over ten times more frequently in the SuS (18/640 = 2.8%) than in the SuN (18/7540 = 0.2%). Koilocytosis (O1) was only observed in a minority of both study groups, but a correlation between koilocytosis and (pre)neoplastic changes could nevertheless be found. In both populations, 17/18 cases of koilocytosis observed occurred in smears with borderline changes (P2-3) and (pre)neoplastic changes (P4-9) (**TABLE 3**). Smears negative for inflammatory changes were diagnosed in 5267/7540 (69.9%) and in 224/640 (35.0%) individuals, respectively.

Discussion

This study shows that fewer dysplasias are present in a high-risk population that has immigrated into a low-risk area for cervical cancer than in the high-risk population continuously living in the high-risk area. This emphasises the significance of environmental factors for differences in the geographical incidence of cervical cancer and its precursors.

Migrant populations are a non-random, self-selected sample of the population of their country of origin, which could give rise to a selection bias when comparing the two. The effect of selection bias is reduced if comparisons can be made between similar groups¹². The Surinamese population in the Netherlands is demographically comparable with that in Suriname^{10,11}. Furthermore, it is unlikely that cervical (pre)neoplastic changes would positively or negatively influence (Surinamese) women's migration behaviour. The vast majority of the Surinamese immigrants lives in urban areas of the Netherlands, which is similar to the situation in Suriname where over 90% of the Surinamese population resides in greater Paramaribo.

We found that the age-adjusted odds for the SuS of developing mild (P4) and moderate to severe dysplasia/neoplasia (P5-9) are higher and increase with (pre)neoplasia grade compared to the SuN (**TABLE 2**). One of the possible causes could be that HPV infection, which precedes cervical dysplasia^{13,14}, is more common in high-risk areas for cervical cancer^{3,15-17}, including Suriname¹⁸. This could be associated with the sexual lifestyle encouraged by the Surinamese culture, as was established in several populations^{8,14,19}. Furthermore, a higher viral load and different HPV type variants in HPV-positive women in a high-risk area could cause an increased risk of cervical cytological abnormalities, as suggested recently²⁰⁻²².

In addition, the fact that the organised screening programme for cervical cancer has only recently started in Suriname could account for the higher outcome in the SuS²³. This is supported by the fact that the majority of the decline in cervical carcinoma incidence rates in developed countries is attributed to the implementation of organised screening programmes². The protective effect of previous screening, independent of HPV, has also been established⁸. One should keep in mind that, in both groups, the (pre)neoplastic changes were observed in low numbers which may unduly influence the odds ratios.

The prevalence of dysplasia in Dutch women is 0.4 % for both mild and moderate to severe dysplasia, which was established in the same region and time frame as the present study²³. A recent study in which cervical smears of multiple immigrant populations in the Netherlands were investigated, revealed a somewhat higher relative risk for mild to severe dysplasia/neoplasia in the immigrant Surinamese smears compared to smears from the Dutch population²⁴. Although the prevalence of dysplasia in Surinamese immigrant women in the Netherlands has decreased, it has not completely diminished to the level of the Dutch women in the Netherlands. This could indicate that they have not

yet completely adjusted their lifestyle to their new environment, especially given that all immigrant Surinamese women in this study are first-generation immigrants. However, we cannot exclude endogenous factors as a possible cause. When feasible, a similar study on the offspring of these immigrants (second generation) could investigate whether the prevalence of dysplasia has further decreased to that of the native Dutch population.

In our study we also found a positive correlation between cytological abnormalities (P2-9) and koilocytosis (O1), which is stronger for the SuS (**TABLE 3**). This confirms a recent study of cervical smears from the Dutch screening programme²⁴ and is also supported by several studies on koilocytosis and cervical carcinogenesis^{25,26}. Koilocytosis is considered to be virally induced and has been correlated with HPV²⁷⁻²⁹. The fact that koilocytosis occurred over ten times more frequently in the SuS suggests a higher prevalence of HPV in this population, which is supported by a recent study¹⁸. It could furthermore be caused by higher viral load or different HPV type variants, as a result of the previously proposed differences in exposure between the high-risk and the low-risk area studied. Koilocytosis can be unequivocally detected in cervical smears and might be an effect of the active stage of HPV infection²⁴. It has been positively correlated to promiscuity, which could explain why a greater number of active HPV infections were observed in the SuS³⁰. In the Dutch population only 4% of the smears with moderate to severe dysplasia also contain koilocytosis²⁴, which may indicate that the HPV infection becomes less active in high-grade lesions. An even lower frequency was observed in the SuN (2%). This is not the case for the SuS where as many as 7/10 of the smears with moderate to severe dysplasia showed koilocytosis, possibly caused by (repeated) reinfection with HPV.

In summary, we have shown that fewer cervical cytological abnormalities are present in a high-risk population that has immigrated to a low-risk area for cervical cancer than in the high-risk population continuously living in a high-risk area. This scenario factors out endogenous differences, as the same ethnic population has been studied in two areas. The findings in this study emphasise the significance of environmental factors, such as HPV exposure. In addition, the presence of an organised screening programme is important. However, endogenous factors and maintained sexual lifestyle should also be considered to be of influence, with the latter related to the fact that the immigrants in this study are first-generation immigrants. The higher frequency of koilocytosis in the women still living in Suriname deserves further study with regard to repeated reinfection with HPV as a cause of the more frequently observed active stage of the infection.

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