Pregnancy and cervical cancer: a retrospective study of the associations of age at first pregnancy and parity with non-invasive and invasive cervical lesions among HIV-negative women in Senegal

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Abstract

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Cervical cancer is the leading cause of cancer-related deaths in Senegal. Senegal's cervical cancer prevention strategy has prioritized vaccinating young girls with human papillomaviruses (HPV) vaccines, but not screening of older women. There is limited knowledge about the roles of age at first pregnancy (AFP) and parity in developing cervical intra-epithelial lesions (CIN) and invasive cervical cancer (ICC) in this population.

We investigated the associations of AFP and parity with CIN and ICC using data from four studies on cervical carcinogenesis conducted in Senegal between 1998 and 2011. Eligibility criteria included not being HIV positive, 18 years or older, not pregnant at visit, and having either histology or cytology results. Missing exposure and covariate data were imputed with Multiple Imputation by Chained Equations using R statistical software. We conducted multinomial logistic regression adjusted for age, age at first sex, birth control method, lifetime

number of male sexual partners, marital status, smoking history, study, site, and visit year to evaluate the associations of CIN and ICC with AFP; live births for parity; and AFP and parity. We did a sub-analysis among those who were positive for any HPV type.

Among the 5,588 women included in this study, the median AFP was 18 years, and the median number of live births was 5. AFP was significantly associated with CIN in the 12-14 (OR=2.01, 95% CI:1.06-3.83) and 15-16 (OR=1.72, 95% CI:1.02-2.88) groups compared to the 21-24 group. Number of live births was associated with CIN and ICC in both the complete and HPV restricted populations, with lower risks in nulliparous group and higher risks in the 3-4, 5-6, and 7+ groups compared to the 1-2 live births group. Parity in the 3-4 live births group was significantly associated with CIN and ICC in the complete population, OR=2.20, 95% CI:1.20-4.02 and OR=1.73, 95% CI:1.10-2.71 respectively; and with ICC in the HPV restricted population, OR=2.26, 95% CI:1.12-4.60. These associations of parity with CIN and with ICC were similar when evaluated along with AFP.

Early AFP increases risk of CIN and higher parity increases risk of ICC among HIV-negative women in Senegal. The effect of AFP and parity on CIN and ICC are independent of each other when assessed with confounding. These findings can inform future cancer prevention and screening strategies.

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Introduction

Cervical cancer is the fourth most common and most deadly cancer among females, accounting for 604,000 cases and 342,000 deaths in 2020 globally[1,2]. Persistent infection with human papillomaviruses (HPV) has been identified as the causative agent, with high-risk HPV types 16 and 18 responsible for 70% of all cervical cancer cases[2]. About 85% of the global cervical cancer morbidity and mortality burden is borne by low-and-middle income countries (LMICs)[3]. This disparity has been attributed to the absence or late introduction of national HPV immunization programs, low screening rates, and limited cancer treatment options in these countries[4]. While there have been improvements in the introduction of vaccines in LMICs, other preventive strategies have lagged. Furthermore, challenges in vaccine implementation, such as limited funding and narrow eligible age cohorts (9-13 years) reduce vaccine uptake and could delay declines in cancer rates by several decades[4].

Cervical cancer is rare relative to the high prevalence of HPV infection, suggesting that there are co-factors associated with HPV persistence and progression to cervical cancer [5,6]. Pregnancy-related factors such as multiparity, age at first pregnancy and age at first sexual intercourse have been reported to be associated with increased cervical cancer risk; however, there are variations in the strength and direction of these associations reported across studies and populations. Biologically, it is possible that risk factors are linked to either increased progesterone and estrogen levels during pregnancy or changes in cervical tissue during puberty and birth, which can lead to an increased risk of persistent HPV infection and carcinogenesis[5–7].

Few studies have investigated these associations in Sub-Saharan Africa. Muwonge et al.[6] conducted the largest study of these associations in Sub-Saharan Africa using screening data across 7 countries (n=47,361) and found a strong association of high parity with high grade lesions and cervical cancer. Although they could not assess the association with age at first pregnancy, in other research, age at first pregnancy is correlated with age at marriage, the latter of which was inversely associated with invasive cervical cancer. Three smaller studies (n<260) conducted in Mali[8], Ethiopia[9], and Ivory Coast[9] also found an association with parity, although only the first considered the effect of HPV infection. However, none of the four studies controlled for the confounding effects of smoking, sexual history, birth control use, or HIV status, all of which have been associated with cervical carcinogenesis[10].

In Senegal, cervical cancer is the overall leading cause of cancer-related mortality with 1,312 deaths recorded in 2020[3,5]. The country has made substantial progress in introducing the HPV vaccine in its routine immunization program. However, it faces similar challenges as other LMICs discussed above. The high HPV prevalence (12.5%-30.3%[11]) in the country necessitates an investigation into the co-factors of cervical carcinogenesis in this population where HIV prevalence is low. This study will therefore investigate the pregnancy-related associations without the confounding role of HIV infection in Senegal. Specifically, we aim 1) to determine the associations of age at first pregnancy with invasive cervical lesions and with pre-invasive cervical abnormalities and 2) to determine the associations of parity with invasive cervical lesions and with pre-invasive cervical lesions. We hypothesize that earlier age of first pregnancy will be associated with invasive and pre-invasive cervical abnormalities due to the additive effects of HPV infection and hormonal exposure on a developing and susceptible cervix and that higher parity will have a strong association with invasive and pre-invasive cervical abnormalities due to multiple elevated hormonal and physiologic changes from pregnancy.

Methods

Data Sources

We conducted secondary analyses using screening and diagnostic data collected in Senegal between 1998 and 2011. The data were collected by four studies- Epidemiology and Biology of HIV Positive & Negative Cervical Neoplasia (Epi/Bio)[12], Developing New Approaches to Cervical Cancer Control (New Approaches)[13], HIV-Associated DNA Hypermethylation in Cervical Cancer (Hypermethylation)[14], and Chlamydia and Aberrant DNA Methylation in Cervical Cancer (Chlamydia)[15]. The first three studies investigated the oncogenesis of neoplasia associated with HIV, while the fourth study investigated oncogenesis of neoplasia associated with C. trachomatis infection among HPV positive individuals.

Participants were enrolled across three different hospitals within the Dakar Region- a cancer referral hospital in Dantec, an outpatient primary clinic in Pikine, and an outpatient infectious disease clinic in Fann. The New Approaches and Epi/Bio studies did not enroll participants in Fann and Pikine respectively. Only subjects enrolled in Dantec had symptoms for cervical cancer prior to enrollment in these studies. Trained medical staff conducted structured interviews with participants to obtain socio-demographic and medical history information. Participants were tested for HIV and HPV followed by screening or diagnostic tests for cervical abnormalities with cytology and/or histology.

Study Population

Subjects were eligible for this study if they did not have a positive test result for HIV. This criterion included those who tested negative for HIV (n=3,944) and those who were not tested for HIV (n=1,644) but were classified as HIV negative due to the low prevalence of HIV in Senegal. Other eligibility criteria included being 18 years and older, not pregnant at time of study recruitment and having cervical histology and/or cytology test results. None of the women in this study identified as commercial sex workers. For participants with multiple study visits, the observations from the first visit were used.

Definitions

Three cervical outcomes were defined based on cervical histology or cytology. Histology results were used as the gold standard such that it was used to determine outcome status if was available for a subject, otherwise cytology results were used. Normal cervical outcome was defined as negative, atypical squamous cells (ASCUS), or other atypical histology results if available; otherwise, it was defined as either negative, ASCUS or other atypical cytology results. Pre-invasive cervical outcome was defined using histology results of CIN1 (cervical squamous intraepithelial neoplasia 1), CIN2–3, carcinoma in situ (CIS), adenocarcinoma in situ (AIS); or using cytology results of low grade or high grade squamous intraepithelial lesion (LSIL or HSIL), CIS, AIS. Invasive cervical cancer, ICC, was defined as having either histology or cytology results of squamous cell carcinoma or adenocarcinoma.

The main exposures for this study were age at first pregnancy (AFP) and parity. Age at first pregnancy was defined as the age at which a participant first became pregnant. Age at first pregnancy for those who were ever pregnant was categorized as 12-14, 15-16, 17-20, 21-24, and greater than 24. Parity was primarily assessed by the number of live births a participant had prior to enrolment. This measure is limited as it does not account for still births, miscarriages, and elective terminations which could be full- or almost- term pregnancies. Therefore, we also evaluated gravidity, the number of times ever pregnant, and pregnancy loss, the difference between gravidity and live births, to better assess parity. Live births and gravidity were each categorized as 0, 1-2, 3-4, 5-6, and 7 or greater live births or pregnancies, while pregnancy loss was evaluated as a continuous variable.

Multiple Imputation

There was substantial missingness in our pooled dataset as some variables were not collected or were collected during follow-up visits by some of the primary studies. Missingness in our primary exposures ranged from 1.3% for number of live births, 0.8% for number of pregnancies and 5.4% for age at first pregnancy. Education level had the most missingness (74%), followed by 31-36% missingness in age at first sex, smoking, alcohol use, and birthplace. All other covariates had less than 18% missingness.

We imputed missing values in the exposures and covariates to overcome possible bias associated with non-random missingness and reduced power and efficiency of the study with complete-case analysis. We used Multiple Imputation by Chained Equations (MICE), which performs well with both categorical and continuous variables and with non-monotonic missingness, to overcome the limitations of complete case analysis. MICE was done with 20 imputed datasets over 200 iterations to obtain complete datasets and reduce the uncertainty of a single imputation. The imputation model included all analytic variables and a non-analytic variable, age at first menstrual period. We excluded education from our imputation model as we were concerned that the high percentage of missingness would bias the imputed values. The prediction matrix was modified such that collinear variables (correlation coefficient > 0.7) could not be used to predict each other. The imputation models were dependent on the data type of the variables: logistic regression for binary variables, polytomous logistic regression for categorical variables, and predictive mean matching for integer continuous variables.

Statistical Analyses

We conducted multinomial logistic regression to evaluate the associations of ICC and pre-invasive lesions with AFP and with parity. Associations were estimated as odds ratios (OR) and 95% confidence using Wald tests. We used five primary models for this study- one with AFP as the main exposure; three separate models for parity including live births, pregnancy, and live births and pregnancy loss as main exposures; and a final joint model that included AFP, live births and pregnancy loss as main exposures. Three analyses were used to evaluate these associations; crude analyses that evaluated the associations of each exposure with ICC and with pre-invasive lesions; adjusted analyses that evaluated the association of each exposure and set of confounders with ICC and with pre-invasive lesions in the full population; and adjusted analyses that were restricted to subjects who had tested positive for HPV (any type). All analyses were performed in RStudio using R statistical software (version 4.1.1).

We selected age, smoking history (ever/never), age at first sex, birth control method (none/hormonal/condoms/other non-hormonal), lifetime male sex partners, and marital status *a priori* as confounders based on literature review. We also evaluated ethnicity (Wolof/Pulaar/Serere/Other), current alcohol use (yes/no), positive for multiple HPV types, study, visit year, and site as confounders by assessing if they changed the crude OR estimate by 10% or more. Study, visit year, and site met this criterion and were included in the adjusted model.

Results

Baseline characteristics of the 5,588 subjects in this study are summarized in Table 1. The median age of the study population was 44 years, ranging from 18 to 90 years. There was a low prevalence of ever smoking (0.8%) and current alcohol use (1.1%), and the median lifetime number of male sexual partners was 1 with a range of 0 to 35. 5,373 (97%) had been pregnant before and the median age at first pregnancy was 18 years ranging from 12 to 42 years. Median number of pregnancies was 7 (range: 0-19) and median number of live births was 5 (range: 0-16).

Among our study subjects, 328 (5.9%) and 1,024 (18.3%) had pre-invasive and invasive cervical lesions respectively. The distribution of low grade (LSIL/CIN1) and high grade (HSIL/CIN2-3/CIS) lesions was almost even in the pre-invasive lesions group, with 158 (48.2%) having high grade lesions (data not shown). 978 (94.8%) of those with ICC were enrolled at the cancer referral clinic in Dantec. Median age among subjects with ICC (50 years) was higher than in those with pre-invasive lesions and normal cervix (43 years). 81.6% of those with ICC reported never having any formal education compared to those with pre-invasive lesions (60.5%) and normal cytology (64.7%). Furthermore, compared to either those with pre-invasive or with no lesions, subjects with ICC initiated sexual activity at a lower age (median age 16 vs 17 years). The percentage of those who did not use any form of birth control was higher among those with ICC (94.6%) compared to those with pre-invasive (71.2%) and no cervical abnormalities (74.7%). Similarly, HPV positivity was higher in those with ICC (83.4%) compared to those with pre-invasive (58.2%) and no cervical abnormalities (21.3%).

Age at First Pregnancy

Age at first pregnancy was lowest among women with ICC (median: 17 years) compared to those with pre-invasive lesions and no lesions (18 years). The associations of AFP and ICC as well as AFP and pre-invasive lesions are summarized in Table 2. Among women who were ever pregnant, age at first pregnancy was associated with ICC in the unadjusted analysis. There were significantly higher odds of having ICC in the 15-16 (OR= 1.89, 95% CI: 1.42-2.51) and 17-20 (OR= 1.81, 95% CI: 1.38-2.27) age groups but significantly lower odds in the 25+ age group (OR= 0.58, 95% CI: 0.39-0.87), when compared to the 21-24 age group. Although there was a similar trend in the associations of AFP with ICC in both the complete and HPV restricted adjusted analyses, none were significant.

In contrast, AFP was significantly associated with pre-invasive lesions in the complete adjusted analysis, but not in the crude and adjusted HPV restricted analyses. In the complete adjusted analysis, the odds of ICC were significantly higher in the 12-14 (OR= 2.01, 95% CI: 1.06-3.83) and 15-16 (OR= 1.72, 95% CI: 1.02-2.88) groups.

Parity

Median number of live born infants was the same (5) in all outcome groups. However, median number of pregnancies (8) and pregnancy losses (2) were highest in the ICC group compared to pre-invasive and normal groups (7 pregnancies and 1 pregnancy loss). The associations of live births, pregnancies and pregnancy loss with ICC and pre-invasive lesions are summarized in Table 3.

Across all three analyses, the number of live births was significantly associated with ICC, as there were lower risks in nulliparous group and higher risks in the 3-4, 5-6, and 7+ groups compared to the 1-2 live births group. Only the associations in the 3-4 group were significant in the adjusted analyses among the complete (OR=1.73, 95% CI: 1.10-2.71) and HPV restricted (OR=2.26 ,95% CI: 1.12-4.60) populations. The number of pregnancies was similarly significantly associated with ICC, with stronger associations across most groups than that of number of live births and ICC and statistically significant associations in the 5-6 groups of the adjusted analyses.

In investigating the effect of number of pregnancy losses while accounting for number of live births, the odds of ICC was 1.09 times higher with each additional increase in pregnancy loss (95% CI: 1.05-1.13). Although this association was similar in the adjusted analyses, none were significant. Furthermore, the associations of number of live births and ICC across all 3 analyses were similar to the associations in the models without number of pregnancy losses.

Numbers of live births and pregnancies were not associated with pre-invasive lesions in either the crude or adjusted analyses in the complete population. When restricted to the HPV positive population, the adjusted associations were significant in the 3-4 group (OR=2.20, 95% CI: 1.20-4.02) for number of live births as well as the 5-6 (OR=2.2, 95% CI:1.04-4.64) and 7+ (OR=1.73, 95% CI:1.03-4.33) groups for number of pregnancies. Pregnancy loss was not significantly associated with pre-invasive lesions in any of the models.

Joint Analyses

When assessed along with parity and pregnancy loss, we found that among women that were ever pregnant, there was a significant association of AFP with ICC in the crude analysis but not in either of the adjusted analyses (Table 4). Although these associations in the crude analysis were significant for the same groups (i.e., 15-16, 17-20, and 25+), they were slightly weaker than those of the independent association of AFP.

Number of live births was no longer significantly associated with ICC when accounting for AFP and number of pregnancy losses in the crude model compared to the independent model with just live births. However, it remained significantly associated with adjusted analyses with higher odds of ICC in the 3-4 group of the complete and HPV restricted populations. As in the independent model, number of pregnancy losses was significantly associated with ICC in the crude analysis with similar associations, but not in the adjusted analyses.

In the joint model, AFP had slightly stronger significant associations with pre-invasive lesions in the adjusted analysis of the complete population, but these were significant in the other two analyses. Number of live births was only associated with pre-invasive lesions in the HPV restricted analysis, with a weaker significant association in the 3-4 group (OR=2.12, 95% CI: 1.15-3.93) compared to their association from the independent model. The associations of number of pregnancy losses with pre-invasive lesions in all three models were marginal and statistically insignificant.

Discussion

To our knowledge, this is first study in Senegal and one of the few studies in Sub-Saharan Africa to investigate the associations of age at first pregnancy and parity with invasive and with pre-invasive cervical lesions. Our results suggest that a higher number of live births increases risk of developing ICC, while early age at first pregnancy increases risk of developing low- and high- grade cervical lesions among HIV-negative women in Senegal. These results are concordant with the results of similar studies in non-HIV restricted populations and strengthen evidence for the role of multiparity and age at first pregnancy on cervical carcinogenesis.

The mechanisms by which pregnancy is associated with invasive and pre-invasive cervical lesions have been comprehensively described in literature. Briefly, physiologic, hormonal, and immunologic changes due to pregnancy can increase susceptibility to HPV infection and other co-factors and weaken immunologic response to HPV infections. Most cervical cancers originate from the transformation zone (TZ), which is at the intersection of the endocervix and ectocervix. The TZ is made up of glandular cells from the endocervix and squamous cells from the ectocervix[16,17]. Increased levels of estrogen during pregnancy, particularly during the last two trimesters of pregnancy, as well as during adolescence can lead to the eversion of the endocervical lining (cervical ectopy) into the vaginal canal[10,16,17]. This exposes the TZ to the acidic environment of the vagina, triggering the transformation of glandular cells into squamous cells (squamous metaplasia)[10,17]. Infection with oncogenic HPV viruses can disrupt this process, resulting in abnormal cells that may then proliferate into pre-invasive lesions and cancer[10,16,17]. Squamous metaplasia also increases vulnerability to HPV infection as it exposes cells to HPV infection and promotes viral replication[17]. In addition, elevated estrogen levels play a role in down-regulating immune response to HPV infection, leading to HPV persistence [7,18,19], while also working with HPV oncoproteins to promote carcinogenesis[20,21].

Age at First Pregnancy

Age at first pregnancy was somewhat associated with ICC in the crude, adjusted, and adjusted HPV restricted analyses, but the associations were not significant in any of adjusted analyses. This differs from previous studies[7,22–24] which found a significant association between AFP and ICC, but is similar to the large, pooled case-control study conducted by the International Agency for Research on Cancer (IARC) across 8 countries[10]. The loss of significance after adjusting for confounding raises the possibility of over adjustment, as we adjusted for age at first intercourse which is highly correlated with age at first pregnancy in our pooled dataset (Spearman correlation coefficient = 0.75). Interestingly, the association of AFP with pre-invasive lesions was stronger and significant when controlled for confounding in the complete population compared to the univariate association. Taken together, these results suggest that early pregnancy is associated with the development, persistence, and progression of cervical lesions.

Early age at first pregnancy could increase the risk of dysplasia and cervical cancer through cervical and hormonal changes occurring during adolescence and pregnancy. Estrogen-stimulated cervical ectopy and neoplasia are most pronounced during first pregnancy[7] and could therefore be more relevant during adolescence. Increased hormonal levels and physiologic changes during adolescence could therefore also increasing susceptibility to HPV, impair immune response for HPV clearance, and promote cervical dysplasia and cancer.

The lack of significant associations in our study could be explained by several factors. Firstly, the first pregnancy may not necessarily be full-term such that hormone levels never reach the levels needed or were elevated long enough to promote and sustain oncogenesis. In addition, early termination of a pregnancy interrupts the hormone-mediated immune suppression and HPV persistence, allowing lesions to regress. Lastly, HPV infections are more transient in younger groups among immunocompetent populations as they are more likely to clear the infection[25,26] . This is supported in our study as contrary to what would be expected, the risks of pre-invasive lesions and ICC with AFP in the HPV-positive restricted population were weaker than those of the overall population. This suggests that current HPV infection may be less of an important factor than HPV infection at first pregnancy in the association between early AFP and ICC.

Parity

In the current study, we found that the risk of pre-invasive lesions and ICC increased with higher numbers of live births. These risks were stronger among those with HPV. Our findings are consistent with several studies that found strong associations of pre-invasive lesions and ICC with increasing parity across different populations[6,8,27], including HPV-restricted populations[10,28]. Prevalence of cervical entropy increases with number of live births and thus high parity exposes the transformation zone to dysplastic and carcinogenic agents for longer periods[10,29] Furthermore, higher parity and possibly higher frequency of parity results in elevated estrogen levels for longer periods. This promotes longer and more frequent estrogen induced HPV persistence[30] and synergy with HPV oncoproteins, resulting in the persistence and progression of cervical lesions[31] that can develop into cancer. Our results support the association of parity with HPV persistence as there are stronger associations between parity and ICC in the HPV restricted population.

The excess risk of ICC and pre-invasive lesions observed with number of pregnancies when compared to that of number of live births can be attributed to the higher numbers of pregnancies and births in this measure, which then lead to more frequent hormonal and physiologic effects of pregnancy on cervical dysplasia and cancer. Interestingly, despite the higher risk of ICC and pre-invasive lesions with pregnancy, number of pregnancy losses was not significantly associated with ICC when assessed along with live births. This result could be attributed to the heterogeneity in the duration of and completion of pregnancies, which included both early terminations (abortions, miscarriages) and late terminations (still births). While there is no consensus on the association of induced abortions and miscarriages on risk of cervical lesions and cancer, Munoz et al. did not find an association between ICC and abortions (defined as all pregnancies terminated before 28 weeks)[10,27,32] .The protective effect of early termination through early regression and HPV clearance could be balanced by the risks associated with longer duration pregnancies that result in still births. The marginal effect of pregnancy loss also raises the possibility that the delivery process itself could also be associated with ICC in this population. Evidence of differences in risk by delivery type (caesarian versus vaginal delivery)[10,33,34] may further explain why there are marginal effects of heterogenous pregnancy loss after accounting for live births. These studies are however limited by the small sample sizes of caesarean deliveries, so the effect of delivery type on cervical neoplasia and cancer remains inconclusive[35].

The lack of significant associations of parity and pre-invasive lesions differs from the literature[27,28,34]. Our inclusion of low-grade lesions, which made up about 50% of the pre-invasive outcome, differs from most studies as they only included medium/high grade or high grade pre-invasive lesions (CIN2, CIN2-3, and CIN3). Muwonge et al. found significant associations of parity with high grade lesions CIN2-3, but not with CIN1[6]. Low-grade cervical lesions have the highest rate of regression among all the cervical abnormalities[36,37], and those developed during pregnancy may be more likely to regress after pregnancy compared to those developed in the absence of parity[37]. Thus, our inclusion of low-grade lesions could have attenuated the association of pre-invasive lesions compared to other studies.

Joint Associations

Our findings for the independent associations of age at first pregnancy and parity with ICC and pre-invasive lesions were generally robust to their inclusion in the same model after adjusting for confounding. This may suggest that AFP and parity are associated with pre-invasive lesions and with ICC via distinct pathways. It further strengthens the evidence that multiparity may be an important factor in the cervical oncogenesis, regardless of possible age-related cervical vulnerability to neoplasia and cancer.

Limitations and Strengths

Our results do not support the hypothesis that there is a consistent trend in the associations of both age at first pregnancy and parity (i.e., higher associations with increasing parity and decreasing AFP). This contrasts with the literature as despite the heterogeneity in the measures and categorization of both parity and age at first pregnancy, there were consistent trends in these associations. We have evidence of threshold effects and a decline in the risk estimates after peaking, which could be due to complete cervical ectopy and residual confounding respectively. There could also be residual confounding through misclassification of the exposures and confounders due to recall bias and errors in the imputation of missing values. In addition, residual confounding may exist due to unmeasured and unassessed confounding. We did not evaluate the effect of socio-economic status on the association of parity with pre-invasive lesions and ICC, as well as how frequency of parity, delivery type and other biological co-factors such as STIs and vaginal infection could have influenced these associations.

Our results are generalizable to populations with low HIV prevalence as we only included subjects who had not tested positive for HIV, whereas other studies in Sub-Saharan

Africa and around the world did not define their study population by HIV status. HIV is a possible confounder in the associations of AFP and high parity with pre-invasive lesions and with ICC. It was found to be associated with early AFP in South Africa[38] and with multiparity in Zimbabwe[39] and Uganda[40]. HIV is also associated with the development and progression of cervical lesions to cervical cancer as it suppresses the immune function, thus increasing susceptibility to HPV function, reactivation of latent HPV infection and HPV persistence[41]. When compared to HIV-negative women in Senegal, HIV positive women had a 69% lower likelihood of HPV clearance[42], as well as twice the rate of progression from HPV to high-grade cervical lesions (HSIL), and lower rates of HSIL regression[14]. Although, the prevalence of HIV is low in this population, the classification of missing HIV data as HIV-negative could have biased our results from what would have been observed in a population that fully tested negative for HIV as HIV status is a potential confounder in the relationships we evaluated. Despite these limitations, this study has several strengths. It is one of the two largest studies in Sub-Saharan Africa to investigate the association of parity and age at first pregnancy and has the largest sample of ICC cases. We were able to retain this sample size by using multiple imputation methods to fill in missing values. This large sample gave us sufficient power to assess finer categorizations of the exposures, including younger AFP categories, than in previous studies. In addition, our data sources have data on demographic, reproductive and sexual history, and HPV status that may not have been previously collected, which enabled us to adjust for them as confounders in the relationships we examined. Lastly, even though live births as a measure of parity does not measure all full-term births, we were able to show that its associations with pre-invasive lesions and ICC were robust when we adjust for pregnancy losses.

Conclusion

Our study has shown that early age at first pregnancy and high parity are independent risk factors for pre-invasive lesions and cervical cancer in Senegal. Knowledge of the associations of parity and age at first pregnancy can help inform prevention strategies to reduce the burden of cervical cancer in a country where early age at first pregnancy and high parity are common. Specifically, intervention points can include social policies that delay pregnancy including keeping girls in school for longer, expanded and accessible family planning services, and introducing screening programs that prioritize early age at first pregnancy and multiparity for HIV-negative women. Future studies could investigate these associations among HIV-positive women as well as evaluate the associations of age at first birth, frequency of births and types of births with invasive and non-invasive cervical lesions.

Tables

Table 1: Demographic, socio-economic, reproductive, and sexual characteristics among Senegalese women between 1998-2011 (N=5,588)

	Normal (N=4,236)	**CIN (N= 328)**	**ICC (N=1,024)**	**Total (N=5,588)**
Age, years				
Median [Min, Max]	43.0 [18.0, 84.0]	43.0 [19.0, 79.0]	50.0 [22.0, 90.0]	44.0 [18.0, 90.0]
Missing	16 (0.4%)	1 (0.3%)	7 (0.7%)	24 (0.4%)
Ethnicity				
Wolof	2210 (62.7%)	164 (60.7%)	440 (45.9%)	2814 (59.2%)
Pulaar	661 (18.7%)	49 (18.1%)	264 (27.6%)	974 (20.5%)
Serere	340 (9.6%)	29 (10.7%)	122 (12.7%)	491 (10.3%)
Other	315 (8.9%)	28 (10.4%)	132 (13.8%)	475 (10.0%)
Missing	710 (16.8%)	58 (17.7%)	66 (6.4%)	834 (14.9%)
Birthplace				
Senegal	2373 (98.4%)	276 (96.5%)	968 (95.5%)	3617 (97.5%)
Other	38 (1.6%)	10 (3.5%)	46 (4.5%)	94 (2.5%)
Missing	1825 (43.1%)	42 (12.8%)	10 (1.0%)	1877 (33.6%)
Education				
None	785 (64.7%)	69 (60.5%)	111 (81.6%)	965 (65.9%)
Primary	384 (31.6%)	41 (36.0%)	24 (17.6%)	449 (30.7%)
Secondary	45 (3.7%)	4 (3.5%)	1 (0.7%)	50 (3.4%)
Missing	3022 (71.3%)	214 (65.2%)	888 (86.7%)	4124 (73.8%)
Ever smoke				
No	2388 (99.2%)	279 (97.6%)	1012 (99.8%)	3679 (99.2%)
Yes	20 (0.8%)	7 (2.4%)	2 (0.2%)	29 (0.8%)

Missing	1828 (43.2%)	42 (12.8%)	10 (1.0%)	1880 (33.3%)
Current alcohol use				
No	2379 (98.8%)	284 (99.3%)	1000 (98.9%)	3663 (98.9%)
Yes	28 (1.2%)	2 (0.7%)	11 (1.1%)	41 (1.1%)
Missing	1829 (43.2%)	42 (12.8%)	13 (1.3%)	1884 (33.7%)
Age at first menstrual period, years				
Median [Min, Max]	15.0 [8.00, 18.0]	15.0 [10.0, 18.0]	14.0 [10.0, 18.0]	14.0 [8.00, 18.0]
Missing	2069 (48.8%)	71 (21.6%)	294 (28.7%)	2438 (43.6%)
Age at first sex, years				
Median [Min, Max]	17.0 [12.0, 38.0]	17.0 [12.0, 33.0]	16.0 [12.0, 40.0]	17.0 [12.0, 40.0]
Missing	1702 (40.2%)	57 (17.4%)	226 (22.1%)	1990 (35.6%)
Marital status				
Single	76 (2.3%)	8 (2.6%)	11 (1.1%)	95 (2.1%)
Married monogamous	1615 (48.4%)	98 (32.5%)	286 (29.2%)	1999 (43.3%)
Married polygamous, 1 co-wife	706 (21.1%)	73 (24.2%)	215 (22.0%)	994 (21.5%)
Married polygamous, ≥ 2 co-wives	473 (14.2%)	72 (23.8%)	176 (18.0%)	721 (15.6%)
Separated	256 (7.7%)	22 (7.3%)	66 (6.7%)	344 (7.4%)
Widowed	214 (6.4%)	29 (9.6%)	224 (22.9%)	467 (10.1%)
Missing	896 (21.2%)	26 (7.9%)	46 (4.5%)	968 (17.3%)
Lifetime number of male sexual partners				
Median [Min, Max]	1.00 [0, 35.0]	1.00 [1.00, 10.0]	1.00 [1.00, 10.0]	1.00 [0, 35.0]
Missing	744 (17.6%)	71 (21.6%)	148 (14.5%)	963 (17.2%)

Birth control method				
None	3142 (74.7%)	232 (71.2%)	952 (94.6%)	4326 (78.1%)
Hormonal	666 (15.8%)	62 (19.0%)	41 (4.1%)	769 (13.9%)
Condoms	25 (0.6%)	5 (1.5%)	3 (0.3%)	33 (0.6%)
Other Non-hormonal	375 (8.9%)	27 (8.3%)	10 (1.0%)	412 (7.4%)
Missing	28 (0.7%)	2 (0.6%)	18 (1.8%)	48 (0.9%)
Pregnancies				
Median [Min, Max]	7.00 [0, 19.0]	7.00 [0, 15.0]	8.00 [0, 18.0]	7.00 [0, 19.0]
0	153 (3.6%)	9 (2.8%)	7 (0.7%)	169 (3.0%)
1-2	426 (10.1%)	27 (8.3%)	66 (6.6%)	519 (9.4%)
3-4	577 (13.7%)	46 (14.2%)	107 (10.7%)	730 (13.2%)
5-6	812 (19.3%)	57 (17.6%)	193 (19.3%)	1062 (19.2%)
7+	2248 (53.3%)	185 (57.1%)	629 (62.8%)	3062 (55.3%)
Missing	20 (0.5%)	4 (1.2%)	22 (2.1%)	46 (0.8%)
Live births				
Median [Min, Max]	5.00 [0, 16.0]	5.00 [0, 13.0]	5.00 [0, 13.0]	5.00 [0, 16.0]
0	233 (5.6%)	14 (4.3%)	22 (2.2%)	269 (4.9%)
1-2	638 (15.2%)	38 (11.8%)	130 (13.0%)	806 (14.6%)
3-4	868 (20.7%)	74 (22.9%)	219 (21.9%)	1161 (21.1%)
5-6	1102 (26.3%)	92 (28.5%)	260 (26.0%)	1454 (26.4%)
7+	1348 (32.2%)	105 (32.5%)	370 (37.0%)	1823 (33.1%)
Missing	47 (1.1%)	5 (1.5%)	23 (2.2%)	75 (1.3%)
Number of pregnancy losses				
Median [Min, Max]	1.00 [0, 15.0]	1.00 [0, 7.00]	2.00 [0, 12.0]	1.00 [0, 15.0]
Missing	47 (1.1%)	5 (1.5%)	23 (2.2%)	75 (1.3%)

Ever Pregnant				
No	153 (3.6%)	9 (2.8%)	7 (0.7%)	169 (3.0%)
Yes	4063 (96.4%)	315 (97.2%)	995 (99.3%)	5373 (97.0%)
Missing	20 (0.5%)	4 (1.2%)	22 (2.1%)	46 (0.8%)
Age at first pregnancy, years				
Median [Min, Max]	18.0 [12.0, 42.0]	18.0 [13.0, 33.0]	17.0 [13.0, 42.0]	18.0 [12.0, 42.0]
12-14	371 (9.3%)	30 (9.9%)	64 (7.8%)	465 (9.1%)
15-16	937 (23.4%)	72 (23.7%)	236 (28.9%)	1245 (24.3%)
17-20	1713 (42.8%)	143 (47.0%)	419 (51.2%)	2275 (44.4%)
21-24	518 (12.9%)	35 (11.5%)	68 (8.3%)	621 (12.1%)
25+	464 (11.6%)	24 (7.9%)	31 (3.8%)	519 (10.1%)
Missing	80 (2.0%)	15 (4.7%)	199 (19.6%)	294 (5.4%)
HIV status				
Negative	2625 (100%)	298 (100%)	1021 (100%)	3944 (100%)
Missing	1611 (38.0%)	30 (9.1%)	3 (0.3%)	1644 (29.4%)
HPV status				
Negative	3270 (78.7%)	132 (41.8%)	138 (16.6%)	3540 (66.7%)
Positive	887 (21.3%)	184 (58.2%)	694 (83.4%)	1765 (33.3%)
Missing	79 (1.9%)	12 (3.7%)	192 (18.8%)	283 (5.1%)
Positive for multiple HPV types				
No	3885 (93.5%)	255 (80.7%)	635 (76.2%)	4775 (90.0%)
Yes	272 (6.5%)	61 (19.3%)	198 (23.8%)	531 (10.0%)
Missing	79 (1.9%)	12 (3.7%)	191 (18.7%)	282 (5.0%)
Recruitment site				
Dantec [diagnostic clinic]	334 (7.9%)	74 (22.6%)	978 (95.5%)	1386 (24.8%)

Fann [screening clinic]	324 (7.6%)	25 (7.6%)	11 (1.1%)	360 (6.4%)
Pikine [screening clinic]	3578 (84.5%)	229 (69.8%)	35 (3.4%)	3842 (68.8%)
Study				
Chlamydia/Hypermethylation	1674 (39.5%)	89 (27.1%)	315 (30.8%)	2078 (37.2%)
Epi/Bio	2298 (54.2%)	207 (63.1%)	339 (33.1%)	2844 (50.9%)
New Approaches	264 (6.2%)	32 (9.8%)	370 (36.1%)	666 (11.9%)
Visit year				
1998-2000	1998 (47.2%)	139 (42.4%)	221 (21.6%)	2358 (42.2%)
2001-2006	610 (14.4%)	108 (32.9%)	488 (47.7%)	1206 (21.6%)
2007-2011	1628 (38.4%)	81 (24.7%)	315 (30.8%)	2024 (36.2%)

Table 2: Associations of age at first pregnancy (AFP) with invasive and pre-invasive cervical lesions among ever pregnant Senegalese women between 1998-2011, N=5,417

Age at first pregnancy	**Crude OR (95% CI) N=5,417**		**Adjusted[1] OR (95% CI)**			
			Overall N=5,417		**HPV Positive N=1,889**	
	CIN n=318	ICC n=1,016	CIN n=318	ICC n=1,016	CIN n=185	ICC n=839
12-14	1.18 (0.72-1.95)	1.37 (0.95-1.96)	**2.01 (1.06-3.83)**	1.52 (0.71-3.28)	1.38 (0.54- 3.52)	1.26 (0.35-4.56)
15-16	1.12 (0.74-1.70)	**1.89 (1.42-2.51)**	**1.72 (1.02-2.88)**	1.71 (0.93-3.13)	1.03 (0.48-2.21)	0.93 (0.34-2.58)
17-20	1.21 (0.82-1.78)	**1.81 (1.38-2.27)**	1.52 (0.997-2.31)	1.55 (0.95-2.54)	1.22 (0.66-2.26)	1.20 (0.53-2.74)
21-24	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
25+	0.75 (0.44-1.28)	**0.58 (0.39-0.87)**	0.58 (0.32-1.07)	0.63 (0.32-1.25)	0.36 (0.12-1.06)	0.60 (0.19-1.89)

[1] Adjusted for age, age at first sex, birth control method, lifetime number of male sexual partners, marital status, smoking history, study, site, and visit year.

Table 3: Associations of parity measures with invasive and pre-invasive cervical lesions among Senegalese women between 1998-2011, N=5,588

Parity Measures	**Crude OR (95% CI) N=5,588**		**Adjusted[1] OR (95% CI)**			
			Overall N=5,588		**HPV Positive N=1,939**	
	CIN n=328	ICC n=1,024	CIN n=328	ICC n=1,024	CIN n=190	ICC n=844
Live births						
Nulliparous	0.98 (0.52-1.84)	**0.46 (0.29-0.73)**	1.01 (0.52-1.94)	0.54 (0.25-1.13)	0.87 (0.34-2.23)	0.47 (0.15-1.46)
1-2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
3-4	1.40 (0.93-2.10)	1.24 (0.98-1.58)	1.50 (0.98-2.29)	**1.73 (1.10- 2.71)**	**2.20 (1.20-4.02)**	**2.26 (1.12-4.60)**
5-6	1.37 (0.93-2.02)	1.17 (0.92-1.47)	1.48 (0.97-2.25)	1.16 (0.75- 1.80)	1.71 (0.93-3.12)	1.51 (0.77-2.97)
7+	1.28 (0.87-1.87)	**1.36 (1.09-1.69)**	1.33 (0.86-2.06)	1.20 (0.75- 1.80)	1.82 (0.97-3.41)	1.24 (0.63-2.44)
Pregnancies						
0	0.98 (0.45-2.13)	**0.30 (0.13-0.67)**	1.12 (0.50-2.51)	0.32 (0.09-1.11)	1.32 (0.41-4.30)	0.56 (0.09-3.52)
1-2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
3-4	1.23 (0.75-2.01)	1.21 (0.87-1.69)	1.35 (0.81-2.25)	1.60 (0.89-2.85)	2.11 (0.98-4.56)	**2.70 (1.08-6.72)**
5-6	1.08 (0.68-1.73)	**1.55 (1.14-2.10)**	1.21 (0.73-2.00)	**1.95 (1.11-3.41)**	**2.20 (1.04-4.64)**	**3.48 (1.46-8.30)**
7+	1.27 (0.84-1.92)	**1.83 (1.39-2.41)**	1.36 (0.84-2.20)	1.53 (0.92-2.55)	**2.12 (1.03-4.33)**	2.14 (0.995-4.60)
Live births & Pregnancy loss						
Live births						
Nulliparous	0.98 (0.52-1.83)	**0.47 (0.29-0.75)**	1.00 (0.52-1.93)	0.53 (0.25-1.12)	0.87 (0.34-2.22)	0.45 (0.14-1.39)
1-2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
3-4	1.41 (0.94-2.119)	1.19 (0.94-1.51)	1.52 (0.99-2.32)	**1.72 (1.09-2.69**	**2.24 (1.22-4.11)**	**2.18 (1.07-4.45)**
5-6	1.38 (0.94-2.05)	1.11 (0.88-1.40)	1.49 (0.98-2.26)	1.16 (0.74-1.79)	1.72 (0.94-3.14)	1.49 (0.75-2.94)
7+	1.29 (0.88-1.89)	**1.31 (1.05-1.63)**	1.32 (0.86-2.05)	1.21 (0.78-1.87)	1.81 (0.97-3.40)	1.27 (0.64-2.50)
Number of Pregnancy losses	0.98 (0.92-1.05)	**1.09 (1.05-1.13)**	0.96 (0.90-1.04)	1.02 (0.95-1.10)	0.97 (0.87-1.07)	1.08 (0.95-1.22)

[1] Adjusted for age, age at first sex, birth control method, lifetime number of male sexual partners, marital status, smoking history, study, site, and visit year.

Table 4: Joint associations of age at first pregnancy, live births, and pregnancy loss with invasive and pre-invasive cervical lesions among ever pregnant Senegalese women between 1998-2011, N=5,417

Characteristics	**Crude OR (95% CI) N=5,417**		**Adjusted[1] OR (95% CI)**			
			Overall N=5,417		**HPV Positive N=1,889**	
	CIN n=318	ICC n=1,016	CIN n=318	ICC n=1,016	CIN n=185	ICC n=839
AFP						
12-14	1.21 (0.72-2.01)	1.28 (0.89-1.85)	**2.06 (1.08-3.93)**	1.53 (0.71-3.32)	1.33 (0.52-3.42)	1.16 (0.31-4.36)
15-16	1.13 (0.74-1.73)	**1.79 (1.34-2.39)**	**1.74 (1.03-2.93)**	1.68 (0.91-3.11)	0.98 (0.45-2.12)	0.85 (0.30-2.42)
17-20	1.21 (0.82-1.78)	**1.76 (1.35-2.31)**	1.52 (0.997-2.33)	1.56 (0.94-2.57)	1.18 (0.63-2.19)	1.13 (0.48-2.64)
21-24	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
25+	0.77 (0.45-1.31)	**0.60 (0.40-0.91)**	0.61 (0.33-1.12)	0.65 (0.33-1.30)	0.42 (0.14-1.25)	0.75 (0.23-2.44)
Live births						
Nulliparous	0.92 (0.35-2.46)	0.76 (0.43-1.35)	0.89 (0.33-2.38)	0.80 (0.33-1.96)	0.75 (0.20-2.82)	0.47 (0.12-1.87)
1-2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
3-4	1.35 (0.90-2.03)	1.08 (0.85-1.38)	1.46 (0.95-2.24)	**1.66 (1.05-2.61)**	**2.12 (1.15-3.93)**	**2.21 (1.07-4.55)**
5-6	1.29 (0.87-1.91)	0.96 (0.76-1.22)	1.38 (0.90-2.12)	1.09 (0.69-1.70)	1.58 (0.86-2.93)	1.50 (0.75-3.00)
7+	1.17 (0.79-1.73)	1.06 (0.84-1.34)	1.21 (0.78-1.88)	1.10 (0.70-1.72)	1.70 (0.90-3.21)	1.30 (0.65-2.61)
Pregnancy losses	0.97 (0.91-1.04)	**1.07 (1.03-1.11)**	0.96 (0.89-1.03)	1.01 (0.93-1.09)	0.97 (0.87-1.07)	1.08 (0.96-1.23)

[1] Adjusted for age, age at first sex, birth control method, lifetime number of male sexual partners, marital status, smoking history, study, site, and visit year.

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