Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries

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Early age at first sexual intercourse (AFSI) has long been associated with an increased risk of invasive cervical carcinoma (ICC). Age at first pregnancy (AFP) and ICC have been investigated less, although AFSI and AFP are strongly interrelated in most developing countries. A pooled analysis of case–control studies on ICC from eight developing countries with 1864 cases and 1719 controls investigated the roles of AFSI, AFP, and ICC risk. Age at first sexual intercourse, AFP and age at first marriage (AFM) were highly interrelated and had similar ICC risk estimates. Compared with women with AFSI ≥ 21 years, the odds ratio (OR) of ICC was 1.80 (95% CI: 1.50–2.39) among women with AFSI 17–20 years and 2.31 (95% CI: 1.85–2.87) for AFSI ≤ 16 years (P-trend < 0.001). No statistical interaction was detected between AFSI and any established risk factors for ICC. The ICC risk was 2.4-fold among those who reported AFSI and AFP at ≤ 16 years compared with those with AFSI and AFP at ≥ 21 years. These data confirm AFSI and AFP as risk factors for ICC in eight developing countries, but any independent effects of these two events could not be distinguished.

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Early age at first sexual intercourse (AFSI) has been associated with an increased risk of invasive cervical carcinoma (ICC). Age at first marriage (AFM) is often used as a proxy measure for AFSI, and those who engage in early sexual intercourse may also consequently become pregnant at an early age. Besides early AFSI, early childbearing has also been linked as a risk factor for cervical carcinogenesis and attributed to the cervical trauma experienced during early age at first pregnancy (AFP), or subsequently, by high-parity births (IARC, 2007). The interpretation of the mechanisms by which these sexual and reproductive events occurring early in life might affect ICC risk three or more decades later is not straightforward. The objective of this study is to further characterise and provide robust estimates of the risk of cervical cancer and its association with AFSI, interrelated characteristics such as AFP and AFM in a series of studies that fully considered the association of HPV with cervical cancer.

MATERIALS AND METHODS

The programme of HPV and cervical cancer studies has been coordinated by the International Agency for Research on Cancer (IARC) in Lyon, France and the Institut Catalá d’Oncologia (ICO) in Barcelona, Spain. They included a series of case-control studies on ICC from eight developing countries with a broad range of rates of incidence of cervical cancer that were pooled for analysis. Regions covered include Morocco (Chaouki et al, 1998) and Algeria (Hammouda et al, 2005) in Africa; the Philippines (Ngelangel et al, 1998), Thailand (Chichareon et al, 1998) and...
Madras in Asia; and Brazil (Eluf-Neto et al, 1994), Colombia (Munoz et al, 1993), Paraguay (Rolon et al, 2000) and Peru (Eluf-Neto et al, 1994) in South America. Although Spain (Munoz et al, 1993) was part of the series of case-control studies, the sexual and reproductive behaviour of this population was heterogeneous to the other countries (late AFSI and low parity) and the study site was therefore excluded from this analysis.

The methods of each study have been described elsewhere. Briefly, women with histologically confirmed incident invasive squamous cell carcinoma (SCC), adenocarcinoma or adenosquamous-cell carcinoma were recruited from reference hospitals before treatment. Written informed consent was obtained from those who agreed to participate. Hospital-based controls were frequency-matched to case patients by 5-year age groups.

A standardised questionnaire was administered to the participants by a trained interviewer, which included questions about sociodemographic factors, sexual and reproductive behaviour, smoking habits, pap screening history, hygienic practices, and history of sexually transmitted diseases.

Two samples of cervical exfoliated cells were collected with wooden spatulae and endocervical brushes. After preparation of one Papanicolaou smear, the remaining cells were eluded in saline, wooden spatulae and endocervical brushes. After preparation of history of sexually transmitted diseases.

Two samples of cervical exfoliated cells were collected with wooden spatulae and endocervical brushes. After preparation of one Papanicolaou smear, the remaining cells were eluded in saline, centrifuged and frozen at −70°C until shipment to the central laboratory for HPV DNA testing. A tumour-biopsy sample was obtained from cases and frozen. Cytology and histology diagnoses were reviewed and confirmed by a panel of expert pathologists that agreed on a diagnosis by consensus or majority.

Detailed descriptions of the polymerase-chain-reaction (PCR) assays used in these studies have been described elsewhere. HPV DNA detection was detected by PCR amplification of a small fragment of the L1 gene using MY09 and MY11 consensus primers for the study in Colombia (Hildesheim et al, 1994) and the GP5+/6+ general primer system for the other studies (Walboomers et al, 1992; Jacobs et al, 1995; Roda Husman et al, 1995). β-Globin primers were used to amplify the β-globin gene to assess the quality of the DNA in the specimen. HPV DNA in PCR products was analysed using a cocktail of HPV-specific probes and genotyped by hybridisation with type-specific probes for 33 HPV types. Samples that tested positive for HPV DNA but did not hybridise with any of the type-specific probes were labelled as HPV X.

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI). To assess the association of AFSI with the risk of ICC, three different statistical models to adjust for HPV DNA detection were computed and compared: (1) one model included all patients and controls, and it was not adjusted for HPV DNA status, (2) a second model included all patients and controls, and included a variable to adjust for HPV DNA status, and (3) a third model was restricted to HPV–DNA-positive cases and controls. To control for potential confounding, final models were adjusted for age (<40, ≥40), country, lifetime number of sexual partners (1, >1), parity (0, 1–4, ≥5), and educational level (never, primary, secondary or higher). Each variable included in the adjustment models was assessed for interaction with AFSI. Test for trend was carried out when appropriate, using the log-likelihood-ratio test. Only subjects who reported ever having been married and/or ever having had children were included in the analyses of AFM and AFP.

We evaluated other potential confounding factors such as smoking (never, ever), oral contraceptive use (never, 1–4 years, ≥5 years), history of pap smears excluding those in the 12 months before enrolment (never, ever), having had first sexual intercourse before menarche and the timing of first sexual intercourse relative to age at menarche (data not shown), but they were not adjusted for in the final analysis as they did not contribute any change to the OR estimates for AFSI in the adjusted models.

RESULTS

Table 1 describes some characteristics of the 1864 ICC cases and 1719 corresponding controls that entered the final analysis. Ninety-five percent of case patients and 17% of controls tested positive for HPV DNA. The majority of cases (92%) had SCC. Case patients were older than controls with a median age of 49 vs 48, respectively. Median AFSI was earlier in case patients (17 years) compared with controls (19 years), and this was found to be consistent in each country.

Table 2 shows the risk of ICC by AFSI according to the three different adjustment models. An increased risk of ICC was consistently observed with decreasing AFSI (P-trend <0.001). Compared with AFSI >21 years, the OR of ICC was 1.80 (95% CI: 1.50–2.16) for AFSI 17–20 years, and 2.31 (95% CI: 1.85–2.87) for AFSI ≤16 years, after adjusting for age, centre, lifetime number of partners, parity, and education level in the HPV-unadjusted model. According to the different model adjustments, women reporting AFSI ≤16 years of age had a 2.3–2.5-fold risk of ICC and 1.8–2.1-fold risk for AFSI 17–20 years of age (Table 2). Given the consistent association of AFSI and the risk of ICC across the different models, HPV-unadjusted models were used for the remainder of the results.

We calculated the risk of ICC for each country study, and, in general, each study showed an increasing risk of ICC with decreasing AFSI (data not shown). There was no evidence of heterogeneity with respect to study country (P = 0.58).

| Country  | Cases | Controls | Cases | % | Controls | % | Age a | Cases | Controls | Age at sexual debut a | Cases | Controls |
|---------|-------|----------|-------|----|----------|----|-------|-------|----------|----------------------|-------|----------|
| Country | 1864  | 1719     | 1769  | 94.9 | 285      | 16.6 | 49    | 48    | 17       | 19                   | 49    | 48       |
| Algeria | 142   | 145      | 132   | 93.0 | 18       | 12.4 | 53.5  | 52    | 16       | 18                   | 49    | 40       |
| Morocco | 188   | 176      | 182   | 96.8 | 38       | 21.6 | 48    | 46.5  | 17       | 18                   | 49    | 40       |
| Madras (India) | 187 | 184      | 180   | 96.3 | 51       | 27.7 | 47.5  | 47    | 19       | 21                   | 49.5  | 50       |
| Philippines | 364 | 380      | 349   | 95.9 | 35       | 9.2  | 51    | 52    | 18       | 20                   | 46    | 45.5     |
| Thailand | 378   | 259      | 363   | 96.0 | 41       | 15.8 | 46    | 45.5  | 17       | 18                   | 48    | 48       |
| Brazil  | 187   | 190      | 181   | 96.8 | 32       | 16.8 | 51    | 52    | 18       | 19                   | 48    | 48       |
| Colombia | 110   | 124      | 87    | 79.1 | 21       | 16.9 | 48.5  | 45.5  | 16       | 19                   | 48    | 48       |
| Paraguay | 112    | 86       | 109   | 97.3 | 18       | 20.9 | 48    | 48    | 16       | 18                   | 48    | 48       |

Abbreviation: HPV = human papillomavirus. aMedian.
We stratified the analysis according to the established risk factors for ICC and the positive association of ICC with decreasing AFSI, remained at each level of exposure for each of these characteristics (Table 3). Similar associations were observed for AFP. No interaction was observed between any of the examined risk factors and AFSI. Although not statistically significant, the risk linked to AFSI seemed to be stronger among parous women compared with nulliparous women.

Age at first pregnancy and AFSI were both directly correlated with AFSI in these populations (Pearson correlation coefficient, r = 0.29). Approximately, 92% of women reported AFSI to be the same as APM, One-quarter of women reported AFP to be the same as AFSI. Cumulatively, 62.4% of women reported AFSI and AFP to be the same as AFSI and AFP. Among women with AFSI <16 years, 52.4% were pregnant within the first year of sexual intercourse. Figure 1 shows the high correlation between AFSI and AFP, and the similar decreasing risk of ICC with increasing age of AFSI. Given the high correlation between the two variables, we did not adjust for AFSI or AFP in the AFSI final model and vice versa.

We further evaluated the combined effect of AFSI and AFP on the risk of cervical cancer (Table 4). An increased risk emerged in subsequent strata of decreasing AFP with decreasing AFSI. Given this combined effect, we assessed the latency period (AFP–AFSI) between these two events to clarify whether it affected the cervical cancer risk. Although there was no statistical difference across strata, the data suggested that within each AFSI strata, women with a latency period for a subsequent pregnancy of <2 years may be at a slightly increased risk compared with women with a larger time gap (data not shown).

**DISCUSSION**

The IARC/ICO series of case–control studies remain the largest set of aetiological investigations on ICC that fully addresses the role of HPV DNA and of the independent established cofactors. This is probably also the largest dataset reporting on ICC in the developing world in which early AFSI, AFP and high parity are prevalent phenomenons. The results show that early AFSI and early AFP are risk factors for cervical cancer, irrespective of other known risk factors for the birth. The data presented show a possible additional increase in risk when the early event of first sexual intercourse is shortly followed by a pregnancy.

The mechanism by which the early experience of first sexual intercourse and first pregnancy could influence the risk of cervical carcinogenesis may be explained by the steroid hormonal influence on HPV infection and on the host's immune response to HPV during pre-adolescence and adolescence. The transformation zone of the cervical epithelium has been recognised as the site in which HPV infection tends to cause cancer, and the susceptibility of this area is believed to be related to its denudation of the stratified epithelium, thus facilitating exposure of the basal layer to HPV with minimal trauma. Biological immaturity during adoles-

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**Table 2 Effect of different strategies of multivariate model adjustments on the association between age at first sexual intercourse and risk of ICC (from IARC case–control studies)**

| Sexual debut | Cases n (%) | Controls n (%) | Age and centre adjusted Odds ratio (95% CI) | HPV unadjusted* | HPV adjusted* | HPV-positive only* |
|--------------|-------------|----------------|--------------------------------------------|-----------------|--------------|------------------|
| ≥21 years    | 341 (16.9)  | 656 (35.4)     | 1.00                                       | 1.00            | 1.00         | 1.00             |
| 17–20 years  | 83 (40.2)   | 667 (35.0)     | 2.44 (1.07–2.87)                           | 1.80 (1.50–2.16)| 1.78 (1.32–2.39)| 2.10 (1.49–2.97)|
| ≤16 years    | 710 (35.1)  | 396 (21.4)     | 4.09 (3.38–4.94)                           | 2.31 (1.85–2.87)| 2.09 (1.48–2.96)| 2.48 (1.65–3.73)|

*Adjusted for age, study country, lifetime number of partners (1), parity (0, 1–4, 5), and education (never, primary, secondary).

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Table 3  Age at first sexual intercourse and risk of cervical cancer according to various characteristics

| Characteristics               | Number of cases/controls | Odds ratio (95% CI)a | Odds ratio (95% CI)b | P-trend |
|------------------------------|--------------------------|----------------------|----------------------|---------|
| **Parity**                   |                          |                      |                      |         |
| Nulliparous                  |                          |                      |                      |         |
| ≥ 21 years                   | 14/40                    | 1.00                 | 1.00                 |         |
| 17–20 years                  | 7/14                     | 1.88 (0.53 – 6.66)   | 1.61 (0.40 – 6.57)   |         |
| ≤ 16 years                   | 7/6                      | 3.60 (0.83 – 15.52)  | 1.50 (0.17 – 13.55)  | 0.56    |
| Ever parous                  |                          |                      |                      |         |
| ≥ 21 years                   | 327/614                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 804/645                  | 2.47 (2.07 – 2.94)   | 1.97 (1.63 – 2.36)   |         |
| ≤ 16 years                   | 703/387                  | 4.10 (3.36 – 4.99)   | 2.59 (2.08 – 3.21)   | <0.001  |
| **P-heterogeneity between AFSI and ever parous** | = 0.64                  |                      |                      |         |
| Parity (1–4 births)          |                          |                      |                      |         |
| ≥ 21 years                   | 171/399                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 273/287                  | 2.58 (1.98 – 3.35)   | 1.99 (1.51 – 2.62)   |         |
| ≤ 16 years                   | 169/115                  | 4.72 (3.41 – 6.54)   | 2.71 (1.89 – 3.87)   | <0.001  |
| Parity (> 5 births)          |                          |                      |                      |         |
| ≥ 21 years                   | 156/215                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 531/358                  | 2.01 (1.57 – 2.59)   | 1.71 (1.32 – 2.23)   |         |
| ≤ 16 years                   | 534/272                  | 2.88 (2.19 – 3.78)   | 2.08 (1.55 – 2.78)   | <0.001  |
| **P-heterogeneity between AFSI and parous groups (nulliparous, 1–4 births, and > 5 births)** | = 0.90                  |                      |                      |         |
| Oral contraceptive use       |                          |                      |                      |         |
| Never                        |                          |                      |                      |         |
| ≥ 21 years                   | 218/400                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 453/364                  | 2.33 (1.87 – 2.90)   | 1.77 (1.40 – 2.25)   |         |
| ≤ 16 years                   | 376/184                  | 4.28 (3.29 – 5.35)   | 2.45 (1.82 – 3.29)   | <0.001  |
| 1–4 years                    |                          |                      |                      |         |
| ≥ 21 years                   | 64/162                   | 1.00                 | 1.00                 |         |
| 17–20 years                  | 117/114                  | 2.64 (1.76 – 3.94)   | 1.67 (1.07 – 2.61)   |         |
| ≤ 16 years                   | 111/89                   | 3.94 (2.53 – 6.13)   | 1.95 (1.15 – 3.30)   | 0.01    |
| ≥ 5 years                    |                          |                      |                      |         |
| ≥ 21 years                   | 36/52                    | 1.00                 | 1.00                 |         |
| 17–20 years                  | 124/72                   | 3.26 (1.85 – 5.72)   | 2.46 (1.36 – 4.46)   |         |
| ≤ 16 years                   | 96/49                    | 4.48 (2.39 – 8.40)   | 2.80 (1.38 – 5.65)   | 0.006   |
| Smoking                      |                          |                      |                      |         |
| Never                        |                          |                      |                      |         |
| ≥ 21 years                   | 272/569                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 587/552                  | 2.34 (1.93 – 2.83)   | 1.68 (1.36 – 2.06)   |         |
| ≤ 16 years                   | 550/548                  | 3.76 (3.03 – 4.67)   | 2.06 (1.61 – 2.64)   | <0.001  |
| 1–4 years                    |                          |                      |                      |         |
| ≥ 21 years                   | 67/85                    | 1.00                 | 1.00                 |         |
| 17–20 years                  | 221/113                  | 2.73 (1.81 – 4.13)   | 2.32 (1.50 – 3.60)   |         |
| ≤ 16 years                   | 152/43                   | 3.63 (3.42 – 9.27)   | 3.62 (2.10 – 6.26)   | <0.001  |
| Lifetime number of sexual partners |                      |                      |                      |         |
| Monogamous                   |                          |                      |                      |         |
| ≥ 21 years                   | 270/569                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 529/499                  | 2.33 (1.92 – 2.83)   | 1.80 (1.46 – 2.22)   |         |
| ≤ 16 years                   | 349/214                  | 3.89 (3.05 – 4.96)   | 2.38 (1.83 – 3.11)   | <0.001  |
| Partners > 1                 |                          |                      |                      |         |
| ≥ 21 years                   | 69/74                    | 1.00                 | 1.00                 |         |
| 17–20 years                  | 280/151                  | 2.03 (1.37 – 3.01)   | 1.74 (1.15 – 2.63)   |         |
| ≤ 16 years                   | 352/156                  | 2.75 (1.84 – 4.11)   | 2.14 (1.39 – 3.28)   | 0.001   |
| **P-heterogeneity = 0.36**   |                          |                      |                      |         |
| Education                    |                          |                      |                      |         |
| Never go to school           |                          |                      |                      |         |
| ≥ 21 years                   | 54/57                    | 1.00                 | 1.00                 |         |
| 17–20 years                  | 255/155                  | 1.68 (1.09 – 2.60)   | 1.46 (0.93 – 2.30)   |         |
| ≤ 16 years                   | 402/173                  | 2.41 (1.55 – 3.75)   | 2.09 (1.31 – 3.35)   | 0.001   |
| Primary school               |                          |                      |                      |         |
| ≥ 21 years                   | 164/238                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 404/311                  | 1.99 (1.54 – 2.56)   | 1.62 (1.24 – 2.12)   |         |
| ≤ 16 years                   | 236/167                  | 2.51 (1.87 – 3.39)   | 1.71 (1.24 – 2.36)   | 0.001   |
| Secondary school             |                          |                      |                      |         |
| ≥ 21 years                   | 118/359                  | 1.00                 | 1.00                 |         |
| 17–20 years                  | 150/198                  | 2.68 (1.95 – 3.68)   | 2.29 (1.65 – 3.20)   |         |
| ≤ 16 years                   | 72/55                    | 4.79 (3.07 – 7.47)   | 3.36 (2.07 – 5.47)   | <0.001  |
| **P-heterogeneity = 0.08**   |                          |                      |                      |         |
and experience high parity, making their effects difficult to distinguish from one another. In contrast, results of studies in more developed countries where there is a longer latency period between sexual initiation and AFP, as in Spain, the US (Brinton et al., 1987) or Italy (Parazzini et al., 1989) tend to show an increased risk with early AFSI but not with AFP as first pregnancies tend to occur much later. It is interesting that, in countries like the UK, where the rates of teenage pregnancies are high, women with AFSI of ≤ 17 years had a 2–3-fold increased risk for cervical cancer compared with those with AFSI ≥ 20 years (Green et al., 2003). Consistently, women with an early AFP of 15–19 years had a two-fold increased risk for cervical cancer compared with those with AFP ≥ 25 years (Green et al., 2003). These observations merit further exploration but, in aggregate, tend to indicate a significant increase in risk of neoplastic disease when early AFSI occurs (surrogate of early HPV exposure and a period of increased cervical susceptibility) and is followed closely by an early pregnancy (surrogate of early exposure to high oestrogen levels).

Irrespective of their lifetime number of sexual partners, women have a similar increased risk of ICC with early AFSI as shown by the 2.4-fold risk among monogamous women with AFSI ≤ 16 years as compared with the 2.2-fold risk among women with > 1 lifetime number of sexual partners. It has long been suggested that a cervical cancer risk will also depend on the sexual history of the woman’s male partner in addition to her own behaviour (Skegg et al., 1982). This is particularly relevant in societies where most women are virgins at marriage and monogamous thereafter, where the incidence of cervical cancer for a population may vary depending on the behaviour of the male partner. Of our study women, 70% were monogamous. In several studies among monogamous women, the risk of cervical cancer was reported to be two to eight times for women with husbands who had multiple partners (Pridan and Lilienfeld, 1971; Buckley et al., 1981; Brinton et al., 1989). The sexual history of the male partner was not evaluated in this analysis; however, promiscuity, history of other STIS, and lack of male circumcision are factors that have been associated with the male role in cervical carcinogenesis (Castellsague et al., 2003).

In interpreting our results, we must emphasise the difficulty in fully disentangling a woman’s sexual and reproductive profile in relation to her cancer risk (Schoroder et al., 2003). We cannot exclude misclassification bias if AFSI and the number of sexual partners were inaccurately reported, leading to some residual confounding. However, the presence of established risk factors for ICC, use of oral contraceptives, smoking, and pap smear history did not seem to significantly affect the strength of the association between AFSI, AFP, and risk of ICC.

We examined the different stratified methodologies (unadjusted, HPV-adjusted, and HPV-positive restricted) used to evaluate the association between AFSI and risk of ICC traditionally employed in the literature. This was done to exclude any spurious association related to statistical adjustment and to clarify inconsistent findings of the association found in earlier studies. Although in strict terms restriction of analyses to HPV-positive cases and controls seemed preferable, the consistency of the results across the three different methods provides convincing evidence of the risk associated with AFSI. Furthermore, these results indicate that for the evaluation of other risk factors, adjusting for HPV status is not necessary as the adjustments do not contribute to remove any confounding effect.

Sexual practices in the world indicate that very early intercourse might be occurring in adolescents with 44, 45 and 52% of girls between the ages of 13–19 years reporting being sexually experienced in Argentina, Botswana and Nigeria, respectively.
incidence of cervical cancer; additional efforts are required in family planning and sexual education adapted to the extremely variable sociocultural contexts in the world.

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Conflict of interest

No conflict of interest is declared in relation to this manuscript.
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