Unwanted sexual experiences and cervical cancer

The association between unwanted sexual experiences and early-onset cervical cancer and precancer at age 25 years or less: a case control study.

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25 **Abstract**

26 Background: We examined the association between unwanted sexual experiences and
27 cervical cancer, cervical intraepithelial neoplasia 3, adenocarcinoma *in situ*, diagnosed ≤ 25
28 years of age.

29 Methods: A case-control study of women ≤ 55 years who attended gynaecological hospitals
30 in Australia between 1983 and 2007. Cases were ≤ 25 years when diagnosed with disease,
31 control group 1 were “older women” > 25 years at diagnosis; control group 2 were “well
32 women” ≤ 25 years attending preventive health clinics. A self-administered postal survey was
33 utilised. The main outcome measures were prevalence of childhood sexual abuse (<16 years)
34 and unwanted adolescent sexual experiences (between 16-18 years) in cases compared to
35 controls.

36 Results: Of 400 contactable subjects, 251 participated (62.8%). Prevalence of childhood
37 sexual abuse in cases (26.6% [25/94]) was similar to other groups. Prevalence of childhood
38 genital-contact abuse in cases with cervical cancer was 45.5% [5/11], compared to older
39 women (20% [10/50], $p=0.08$), well women (13.8% [8/58], $p=0.01$); and was marginally
40 more common compared to well women when adjusted for other lifestyle factors (OR 4.7
41 [1.0-22.6], $p=0.05$). Prevalence of unwanted adolescent sexual experiences in cases was
42 28.9% [33/114]. Prevalence of adolescent penile-genital contact experiences in cervical
43 cancer cases was 46.7% [7/15], compared to older women, (9.4%, [6/64], $p<0.001$), and
44 well women 13.7% [10/73], $p=0.003$), and was more common compared to well women
45 when adjusted for lifestyle (OR 5.9 [1.4-24.9], $p=0.02$) and sexual health risk factors (OR 5.6
46 [1.4-22.1] $p=0.01$).

Conclusions: Unwanted sexual experiences with genital contact were a risk factor for invasive cervical cancer ≤ 25 years, likely due to a complex interplay of biological and environmental factors.

Key words: sexual abuse, cervical cancer, young women, human papillomavirus

Introduction

International guidelines have moved towards delayed onset of screening to prevent cervical cancer¹⁻³. This is due to the infrequent occurrence of cervical cancer in younger women, the desire to avoid treatments with potential for obstetric harm for cervical dysplasia which may otherwise naturally regress, and the data suggesting minimal impact on cervical cancer incidence in young women despite screening⁴⁻⁷. Revised cervical screening guidelines from the “Renewal” program were announced in Australia in 2014, with screening commencing at 25 years of age from May 2017⁸. Some have voiced concerns that such a policy may put some young women exposed to sexual abuse at undue harm^{9,10}. It is well documented that earlier age of first sex increases the risk of cervical cancer^{11,12}. Therefore sexual abuse may also increase this risk, potentially through a number of mechanisms. Cervical trauma at a time of epithelial immaturity may facilitate earlier high-risk human papillomavirus (HR-HPV) acquisition and chronic carriage^{13,14}. Furthermore victims of violence are more likely to be exposed to established risk factors for cervical cancer due to maladaptive coping^{15,16,17,18}. These include sexual and reproductive risk factors (earlier sexual debut, increased sexual partners, sex trading, unwanted pregnancy, sexually transmitted infection), and substance abuse (smoking, illegal drugs and alcohol abuse)^{15,16,17,18}. They are also at increased risk of other mental health disorders, including anxiety, depression, post-traumatic stress disorder, and psychosis which may impact on health behaviours¹⁹.

Evidence to guide recommendations for cervical cancer prevention in sexually abused women is sparse. Sexual victimization increases the risk of HR-HPV carriage^{15,20-22}, and there is some evidence to show it increases the risk of cervical cancer in the general population^{16,23,24}. A study of 256 Swedish women with cervical cancer identified from a cancer registry, demonstrated an increased risk of severe sexual abuse (5% vs 2% OR 3.3):

however ‘severe’ abuse was self-defined²³. A study of 204 inmates in Kansas city demonstrated that physical abuse or intimate partner violence increased the risk of an abnormal Pap or cervical cancer on self-report (adjusted OR 5.44), but sexual abuse did not increase risk²⁴. A study of almost 5000 women in Kentucky demonstrated that sexual abuse was associated with self-reported cervical cancer (OR 2.4), but risk was highest in those experiencing all forms of abuse (sexual, physical abuse and intimate partner violence)¹⁶. This strongly suggests that other factors associated with a culture of violence are associated with development of disease, rather than age of first sex, alone. Therefore, studies examining the association between age of first sex and cervical cancer (which largely examine consensual experiences) cannot fully demonstrate the impact of abusive sexual experiences on cervical disease development^{11,12,25}.

Sexually abused women have the potential to carry a disproportionate share of the cervical cancer burden despite the introduction of HPV vaccination. The currently licensed prophylactic HPV vaccines rely on population coverage, with administration prior to exposure. Efficacy declines from 100% to 44% in those already exposed to vaccine related genotypes as compared to those naive from vaccine-related HPV infection²⁶. Furthermore the estimated global prevalence of childhood sexual abuse in females is around 18%²⁷, and there is significant disparity in vaccination coverage rates globally, with the lowest vaccination coverage occurring in resource poor countries that have the highest burden of cervical cancer²⁸.

There have been no specific studies examining the association of sexual abuse and risk for developing cervical cancer at a very young age prior to the age of onset of screening, that could potentially impact on screening guidelines. The aim of this study was to compare the

prevalence of childhood sexual abuse (occurring <16 years) and unwanted adolescent sexual experiences (occurring between 16-18 years) in women diagnosed with invasive cervical cancer, or the precursor lesions cervical intraepithelial neoplasia (CIN) 3, or adenocarcinoma *in situ* (ACIS) at an early-age (≤ 25 years), with women >25 years with the same diagnoses, and in young women (≤ 25 years) attending preventive health and gynaecology clinics. We hypothesized that unwanted sexual experiences with genital contact would be more common in cases.

Materials & Methods

This was a hospital-based, case-control study utilizing a postal survey and chart review of women who attended four major gynaecological oncology centres in three states of Australia.

Case ascertainment. Cases were diagnosed aged ≤ 25 years between 1983 and 2007. We attempted to recruit all cases ≤ 25 with invasive disease. To increase numbers, CIN3 and ACIS, as surrogate endpoints for cervical cancer were also included, an accepted methodology, as used by the WHO²⁹. Analyses were undertaken for all cases (invasive and *in situ*), and where numbers permitted for cases with invasive disease alone (cervical cancer cases) compared to controls. Age 25 years was selected as the case definition cut-off due to delayed cervical screening policies internationally, and as now recommended by the Cervical Screening “Renewal” program in Australia^{1,2,8}.

Control ascertainment. Cases were compared to:

i) “older women” diagnosed with cervical cancer, CIN3 or ACIS > 25 years of age, (control group 1), frequency-matched to cases for year of presentation within 5 years. They were included to minimise differential recall bias by including a group with the same disease classification as the cases;

ii) “well women” ≤ 25 years of age when attending gynaecology clinics (largely Well Women’s Clinics where they attended for preventive health checks, matched to cases for age and year of presentation within 5 years (control group 2).

Subjects in either control group with a history of $\leq$ CIN2 when they were ≤ 25 years, were not excluded due to the high rates of cervical dysplasia and its regression (90%) in young women^{30,31}.

Exclusion criteria from all study groups included those who *i.* were private patients where the treating specialist had not provided consent for contact; *ii.* declined future research involvement, nor postal contact ; *iii.* had moved overseas with no forwarding address; *iv.* had not attended the hospital for the past two years and were not found on the Australian Electoral Roll or telephone directory; *v.* were deceased as determined by linkage to the National Death Index; *vi.* were unable to give consent or were likely to suffer emotional or physical harm as a result of participation³², including those with language difficulties (requiring an interpreter), intellectual disability, recent diagnosis of terminal illness within the last 6 months, unstable psychiatric disorders (psychosis, or depression with suicidal ideation), and active intravenous drug use; or *vii.* were > 55 years of age at the time of recruitment, because of possible inability to accurately recall sexual or reproductive history, and to avoid triggering undue distress in the context of more limited social support³². Those with stable psychiatric disorders such as depression, anxiety, past intravenous drug use, current non-intravenous drug use, were included.

Participants with cervical cancer, CIN3 and ACIS were identified from the hospital medical, pathology and oncology databases using International Classification of Diseases codes with

assistance from the Cancer Council of Victoria for Victorian participants. All subjects ≤ 25 years of age with invasive disease, who did not meet the exclusion criteria, were included in the case pool. Cases with CIN3 and ACIS, and women in the control groups were selected using a random number generator³³.

Subjects were sent a detailed information sheet, consent form, self-administered questionnaire with a reply-paid envelope, and provided with contact details for counselling. Subjects received two additional mail-outs and /or a telephone call before being considered lost to follow-up.

Exposure ascertainment for Childhood Sexual Abuse was determined using a self-administered, itemized childhood sexual experiences survey that adopted standard validated questions on sexual experiences prior to 16 years, based on Fleming³⁴ and Wyatt³⁵ (inter-rater reliability 0.9). Childhood sexual abuse was defined as i. All experiences of sexual contact occurring prior to 16 years with a person ≥ 3 years older, or in any position of authority, irrespective of consent; or ii. Any non-consensual sexual experience with a partner of any age; or iii. An exposure prompting disclosure to counsellors, police, a person of authority or trust; or iv. An exposure prompting a request for counselling through the study; or v. Sexual intercourse prior to 13 years of age irrespective of circumstances. Women who indicated that the age of the other person was within two years of her age, and who did not report to authorities or require counselling, were considered to have experienced a childhood sexual experience, but not childhood sexual abuse. Women who did not provide any further information about the childhood sexual experience were categorized as “indeterminate for childhood sexual abuse” and their results were excluded from the analysis.

Exposure ascertainment for Unwanted Adolescent Sexual Experiences was determined by the Sexual Experiences Survey, a twelve-item self-report instrument, asking about sexual experiences associated with coercion and force³⁶. The survey was preceded by the question ‘Have you experienced any unwanted sexual experiences between the age of 16 and 18?’ and any yes response was considered positive for unwanted adolescent sexual experiences. This methodology was utilized based on an internal consistency reliability of a modified Sexual Experiences Survey in 448 college students of 0.70 for women and 0.89 for men (Cronbach alpha). In a sample of 71 female and 67 male college students, it had a 0.93 one-week, test-re-test reliability³⁷.

Childhood sexual abuse and unwanted adolescent sexual experiences were further categorised into non- mutually exclusive categories, according to severity of the abuse (*i.* non-contact, *ii.* physical contact, *iii.* genital-contact, *iv.* penile-vaginal contact); and also into mutually exclusive groups (*i.* non-penetrative and *ii.* penetrative) (Figure 1). Anyone who had experienced either childhood sexual abuse or unwanted adolescent sexual experiences was categorised as having an “unwanted sexual experience.”

Other key variables. Socioeconomic indices for area (SEIFA) and decile (range 1-10) were determined by the SEIFA Data cubes (2006) from the Australian Bureau of Statistics³⁸. The score is derived from Census variables with a lower score indicating an area of relative disadvantage. The structured questionnaire also asked about history of cervical dysplasia and treatment; medical, sexual, reproductive and lifestyle history. Data were also abstracted from the medical record, which served as cross-validation of survey data.

Statistical analysis. Statistical analysis was performed using STATA IC 11.1 (Statacorp LP, Texas, USA). Categorical variables were compared using χ^2 or Fisher’s exact test, and interpreted as odds ratios (OR), 95% confidence intervals (CI) and p values (alpha level

≤0.05). Continuous variables were assessed using the Wilcoxon-Rank-Sum test. Confounders were defined as those variables which caused a substantial change in the main effect (childhood sexual abuse or unwanted sexual experiences), and that were not in the causal pathway between these experiences and cervical cancer.

Power and sample size

Based on pilot data, the prevalence of penetrative childhood sexual abuse in older women was 15%. There was no pilot data for well women, but previous Australian studies suggested the prevalence of penetrative childhood sexual abuse to be around 6%^{39,40}. A sample size of 207 cases and older women (ratio 1:1) was estimated to detect a true OR of 2.0 for cervical disease in abused compared to non-abused women. The same sample size of well women could detect a true OR for disease of 2.7 (with 80% power and type 1 error of 0.05). To account for loss to follow-up in young women and attrition due to non-eligibility, an excess of cases and well women were selected for chart review (at least double the required sample size).

Results

The overall participation rate was similar for all groups (114/181, 63.0% cases; 64/102, 62.8% older women; 73/117, 62.4% well women, $p=1.0$) (Figure 2). Of the 1272 charts reviewed, cases were less likely to be excluded (128/589, 21.7%) compared to older women (71/217, 32.6%) ($p=0.001$) or well women (172/466, 36.8%) ($p<0.001$). However cases were more likely to be excluded due to risk factors known to be associated with unwanted sexual experiences, such as unstable psychiatric disorders (suicide, psychosis), intravenous drug use, intellectual disability (16/128, 12.4%), compared to well women (2/172, 1.2%) ($p<0.001$).

Demographic data and background risk factors. Median age of presentation was similar in cases and well women (Table 1); however well women (≤ 25 years of age) were slightly younger than cases (≤ 25 years of age with cervical cancer or precancer) at survey completion. Cases and well women were just as likely to have undertaken regular Pap smears prior to 26 years. Cases had higher rates of lifestyle and sexual health risk factors compared to the other groups.

Unwanted sexual experiences in cases (with invasive [n=15] and *in situ* disease [n=99] as a whole group [n=114]) compared to controls: Overall 22.7% (57/251) of subjects met the criteria for childhood sexual abuse (supplementary Table S), and 23.5% (59/251) for unwanted adolescent sexual experiences. The proportion of subjects indeterminate for childhood sexual abuse did not differ between cases (20/114, 17.5%) and older women (14/64, 21.9%) (OR 0.8 [0.3-1.8], $p=0.5$); or well women (15/73, 20.6%) (OR 0.8 [0.4-1.9], $p=0.6$). There was no difference in proportion or severity of childhood sexual abuse experienced by cases and controls (Table 2), even after adjustment for age and year of presentation (data not shown). Cases were more likely to experience unwanted adolescent sexual experiences compared to older women, but not well women matched for age. However there was a trend for unwanted adolescent experiences with penile-genital contact to be more prevalent in cases than well women ($p=0.05$) (Table 2).

Unwanted sexual experiences in cases with invasive disease only [n=15] compared to controls: All cervical cancer cases who experienced childhood sexual abuse, experienced genital-contact abuse (45.5%). Both childhood sexual abuse and unwanted adolescent sexual experiences involving genital-contact were more common in cervical cancer cases compared to the other groups ($p\leq 0.05$) (Table 2).

Circumstances around unwanted sexual experiences with penile-genital contact.

Twenty-eight of the 31 subjects who had experienced childhood sexual abuse with penile-genital contact, provided further information about the circumstances. Median age of onset of penile-genital contact was 10 years (interquartile range [IQR] 5-14) and median duration of contact was 4 years (IQR 2-7) (n=15). The median age difference between the subject and perpetrator was 9 years (IQR 4-30) (n=25). Only a small number of subjects reported circumstances around unwanted sexual experiences with penile-genital contact: median age of initial exposure was 17 years (IQR 16-17) (n=15), median age difference between the subject and perpetrator was 6 years (IQR 2-10) (n=10). Statistical comparisons were not performed due to small numbers.

Proportion of subjects who had experienced any unwanted sexual experience.

Around 37% (93/251) of subjects experienced any unwanted sexual experience (childhood sexual abuse or unwanted adolescent sexual experiences) (Table 2). There was no difference in prevalence between cases (38.6%), older women (34.4%) and well women (37.0%). In cervical cancer cases, the prevalence was 53% (7/15); however this was not significantly higher compared to cases with *in situ* disease (36/99, 36.4%, OR 2.0[0.5-7.0], p=0.2), older women (OR 2.2 [0.6-8.0], p=0.2) or well women (OR 1.9 [0.5-7.0], p=0.2).

Proportion of subjects who had experienced both childhood sexual abuse and unwanted adolescent sexual experiences.

Overall, 10.0% (24/251) of subjects experienced both childhood sexual abuse and unwanted adolescent sexual experiences (cases 14/114 [12.3%], older women 6/64 [9.4%] and well women 5/73 [6.9%]), with no statistical difference between groups (Table 2). The rate of revictimisation was higher in cervical cancer cases (4/15, 26.7%) compared to well women (6.9%, OR 5.0 [0.8-25.5], p=0.02). Results did not reach significance in cervical cancer cases

compared cases with *in situ* disease (10/99, 10.1%, OR 3.2 [0.6-13.7], $p=0.07$) or older women (9.4%, OR 3.5 [0.6-17.5], $p=0.07$).

Risk factors for cervical cancer associated with childhood sexual abuse and unwanted adolescent sexual experiences. Subjects who had unwanted sexual experiences were significantly more likely to experience high-risk exposures that have been previously associated with cervical cancer (Table 3). Genital-contact childhood sexual abuse, and unwanted adolescent sexual experiences with penile-genital contact were included in multivariable regression models. When examining cervical cancer cases and well women, genital-contact childhood sexual abuse was an independent risk factor for cervical cancer at a young age (OR 4.7 [95%CI 1.0-22.6], $p=0.05$) when adjusted for smoking, illegal drug use and alcohol use; but not when adjusted for sexual health risk factors (all $p>0.05$, data not shown). Unwanted adolescent sexual experiences with penile-genital contact was an independent risk factor for cervical cancer at a young age, when adjusted for lifestyle and sexual health risk factors (Table 4).

Discussion

This is the first study examining risk factors for early-onset cervical cancer and precancer in women who are largely outside new cervical screening recommendations^{1,2,8}. An increased prevalence of childhood sexual abuse with genital contact was found in women ≤ 25 years with invasive cervical cancer compared to well women. We cannot establish causation due to the retrospective nature of the study, however we speculate that a biologically plausible mechanism for this finding, is early genital HPV exposure. On the other hand, for cases with only precancerous disease, even more invasive forms of childhood sexual abuse were not significantly increased compared to the control groups. This may be related to the fact that high-grade disease and cervical cancer are distinct entities in young women. High grade

changes are a relatively common and early manifestation of HPV infection in young women related to higher rates of partner change compared to older women^{4,41}. High grade dysplasia is relatively less likely to progress to cervical cancer in young women compared to older women^{42,43}. A ten-year increase in age of diagnosis of CIN3 is associated with a 2.5 fold risk of progression⁴². Hence the profile of young women ≤ 25 years with precancer as opposed to young women who have already developed cervical cancer could be quite distinct.

In developed countries, sexual debut has been occurring at increasingly earlier ages, enabling many years to pass between contact with HPV and onset of screening, and increasing the population risk for cervical cancer and CIN⁴⁴. The HPV vaccine has the potential to be the great equaliser with respect to cervical cancer burden, provided there are high rates of population coverage globally, and administration prior to HPV exposure. In Australia there is high three-dose HPV vaccination coverage (73% across all socioeconomic groups) in our target population of 12-13 years olds⁴⁵. Australian studies have suggested that over 70% of childhood sexual abuse occurs before 12 years, with median age being 10-11 years^{34,46}.

Similarly our study demonstrated that median age of penile-genital contact childhood sexual abuse was 10 years, and occurred in 12% of the total study population. The fact that at least 1 in 10 girls may not receive the full benefit of the vaccine because of potential earlier HPV exposure has not been factored into economic modelling. Furthermore sexual violence is a risk factor for homelessness and disengagement with preventive healthcare and education⁴⁷⁻⁴⁹, which could potentially reduce access to school-based vaccination and appropriate cervical screening in this group.

The association between unwanted adolescent sexual experiences and cervical cancer and precancer is more complex. Both young women with cervical cancer and precancer had a

higher prevalence of these experiences compared to older women with disease, which may in part be related to generational changes. Reported sexual assault rates in Australia have increased by 51% since 1995,⁵⁰ with hazardous drinking and peer abuse being associated factors^{51,52}. Penile-genital contact experiences were more common in cases compared to other groups and the association was stronger in cases with cervical cancer.

We found that comparatively, unwanted adolescent sexual experiences were more strongly correlated to cervical cancer than childhood sexual abuse, and while this sounds counter-intuitive, we speculate that there may be an association due to a number of factors (biological factors, risk factors prior to the experience, maladaptive coping after the experience, and factors related to the perpetrator). HPV exposure at the time of a wider active transformation zone during adolescence may be important for pathogenesis of disease^{53,54}. Children exposed to sexual abuse may have cleared the virus prior to activation of the transformation zone of the cervix where the majority of cervical cancers arise⁵⁵. Pre-existing high-risk factors in some adolescents may contribute. Known predictors of sexual assault include prior sexual assault, psychopathology and familial substance abuse^{52,56}. Accordingly we found that the rate of revictimisation at 16-18 years after experiencing childhood sexual abuse was much higher in cervical cancer cases (27%) compared to well women (6%). Sexual violence in late adolescence can have a more negative impact than in childhood, due to greater awareness of the violation,⁵⁷ potentially increasing the risk further of maladaptive coping, psychopathology, and revictimisation^{18,19,58}. The nature of the perpetrator may also play a role, with abusive partners reported to have higher rates of partner change, less condom use, and higher risk of HPV carriage^{16,59}.

The impact of an unwanted sexual experience on cervical cancer has the potential to be over and above the impact of the early age of first sex alone. Accordingly, we found that unwanted

sexual experiences were strongly associated with previously identified lifestyle and sexual health risk-factors for cervical cancer^{11,12,17,25,60}. When such factors were adjusted for in our analyses, genital-contact childhood sexual abuse was marginally more likely in cervical cancer cases compared to lifestyle factors, but not sexual health factors. Unwanted adolescent sexual experiences with penile-genital contact, was strongly associated with cervical cancer at a young age, when adjusted for both lifestyle and sexual health risk factors. For childhood sexual abuse more significant associations may have been observed with a larger study population. Furthermore, the exclusion of childhood sexual abuse by multivariate analyses may be misleading as sexual health risk-factors may stem from the abuse itself, so may be on the causal pathway between the exposure (childhood sexual abuse), and disease. Therefore it is important to not discount the abuse, as it may be the initiating factor in the path towards disease (Figure 3). While causality cannot be established with this study design, we hypothesize that pathogenesis could be due to a complex interplay of factors: acquisition of high-risk HPV at an early age (the necessary risk-factor)⁶¹, but if it is cleared, then the risk for disease may not be increased. This may potentially account for the high prevalence of abuse in control groups. If there is persistent carriage or secondary acquisition associated with other adverse sexual, reproductive and lifestyle risk factors stemming from the abuse, then risk could be increased.

With delayed onset of cervical screening, some have suggested earlier intervention (such as earlier cervical screening or vaccination) in sexual abuse survivors¹⁰. Potential problems with this approach include the commonality of sexual abuse, high rates of precancerous changes that may otherwise resolve without intervention, along with their obstetric and emotional sequelae, and the cost-effectiveness of screening at a later age without missing large numbers of invasive cancers^{4-7,27,49,62}. Furthermore the majority of childhood sexual abuse is unreported at the time of exposure as children may not have the skills to

communicate what has happened to them, recognise its significance, or may stay silent due to coercion by the perpetrator.^{63,64}

Pragmatic approaches to identification, prevention and management of sexual abuse until further evidence comes to light, may include

- i. providing young women and men with skills for sexual decision making and negotiation;
- ii. educating high risk young women regarding their personal risk for cervical disease;
- iii. increasing training and resources for identification of sexual abuse and for effective counselling to minimise maladaptive coping and revictimisation;
- iv. offering cervical screening from aged 18 years in survivors of sexual abuse with genital contact, where this sensitive information has been elicited;
- v. incorporating the HPV vaccine into forensic protocols, and providing funded vaccination for sexually abused women who do not meet the age criteria;
- vi. supporting at-risk families at the societal level as primary prevention of sexual abuse
- vii. considering sexual abuse as a critical academic priority and working towards introduction of evidence-based health policy and practice. Linkage data between forensic and cytology registries, impact of HPV vaccination on sexual abuse survivors and safety and efficacy of the HPV vaccine within a childhood immunisation program are important areas of consideration.

Limitations of this study include it's retrospective nature. However long term prospective studies to establish causality with cervical cancer have not been undertaken largely related to feasibility. Retention of subjects where prospective follow-up has been attempted has been exceedingly difficult (with one study reporting zero attendees at follow-up)⁶⁵. The low

prevalence of cervical cancer means an impractical sample size would be necessary to observe a sufficient number of cervical cancer case end-points⁶⁶.

A strength of this study was that sexual abuse was measured using very carefully defined criteria, and validation of comorbidities was undertaken by a review of the medical record. However there is no standard definition of childhood sexual abuse due to differing cultural and community standards, and methodology for measurement of sexual abuse in the literature is variable⁶⁷. Sexual abuse studies differ around whether consensuality of the experience is a consideration^{68,69}. In this study, we did not ask if the childhood experiences were “unwanted” as this could have excluded consensual abusive events (due to grooming by the perpetrator). Furthermore, women who meet research criteria for childhood sexual abuse but who do not self-define as such, have been found to subsequently experience more high-risk behaviours and exposures than controls⁷⁰. Some studies define abuse where there is a least a 5-year age difference between the subject and perpetrator^{27,34,69}. However this could inadvertently exclude peer abuse, which contributes up to one third of sex offenses against children³⁴. We used a cut-off of ≥ 3 years consistent with the Victorian Crimes Act⁷¹. Unwanted adolescent sexual experiences were more easily determined, according to non-consensual exposure: therefore no subjects were determined to be ‘indeterminate’ for this. However, a subject may have had a consensual experience with someone in a position of authority, which was not captured.

Another limitation of the study is the small number of cervical cancer cases (with 5/11 experiencing CSA and 7/15 experiencing UASE) which could not allow for detailed evaluation of correlating factors and potential causal mechanisms. Also around 37% of contactable subjects declined participation, consistent with other sexual abuse studies^{35,65,69}.

Participant's experiences may not be representative of non-participants: however reasons for participation were likely similar for cases and controls, enabling comparison between groups.

Inclusion of CIN3/ACIS meant the study assessed a lower-risk case population, however the study benefited from being able to perform the analysis for cases with invasive and *in situ* disease. As the study was hospital-based, findings cannot be generalised to the community.

The well women group may have included some high-risk disadvantaged women, as they are more likely to attend for preventive care in a hospital setting ²⁴. Moreover the prevalence of sexual abuse may have been spuriously lowered in cases, as they were more likely to be excluded for risk factors associated with abuse (unstable psychiatric disorders and substance abuse) ^{18,19}. We also excluded deceased women, who may have been higher risk compared to those alive ¹⁸. Therefore the association between unwanted sexual experiences and cervical cancer may be under-estimated.

Conclusions.

The challenge for cervical cancer prevention in the young, is how to balance benefits versus harms, and to improve detection of those at risk of progressing to cervical cancer prior to the age of commencement of cervical screening, rather than just detecting high grade changes which may regress. This study suggests that unwanted sexual experiences during childhood and adolescence are common experiences in all women; however experiences involving genital-contact may be a potential prognostic factor for invasive rather than *in situ* disease by 25 years. Until more studies are reported, cervical screening requests from survivors of sexual abuse ≥ 18 years, as well as opportunistic HPV vaccination could be considered.

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698 Table 1 Demographic and background information in case group compared to controls

Background	Case n=114	Older women n=64	OR [95% CI] Unadjusted p value ^a cases versus Older women ^b	Well women n=73	OR [95% CI] Unadjusted p value ^a cases versus Well women ^c
Median age presentation years (range) (interquartile range)	23 (18-25) (22-25)	32 (26-45) (28-35)	<0.001	22 (15-25) (21-24)	0.06
Median age at survey years (range) (interquartile range)	30 (23-50) (28-34)	42 (30-55) (37-49)	<0.001 ^b	28 (18-37) (26-30)	<0.001
Ethnicity n (%) Caucasian Asian	113 (99.1) 1 (0.9)	63 (98.4) 1 (1.6)	1.8 [0.0-142], 0.7 ^b	66 (90.4) 7 (9.6)	12.0 [1.5-545], 0.004
Median socioeconomic index for area (interquartile range)	8 (7-9)	8 (6-9)	0.2	8 (7-9)	0.8
Histology n (%) Cervical cancer CIN3/ACIS ^d CIN2 CIN1 No dysplasia	114 (100.0) 15 (13.0) 99 (76.8) 0 0 0	64 (100.0) 13 (20.3) 51 (79.7) 0 0 0		73 (100.0) 0 0 5 (6.8) 12 (16.4) 56 (76.7)	
Undertook Pap smear every 2 years prior to 26 years	82/97 (84.5)	33/53(62.3)	3.3 [1.4-7.8], 0.002	60/73(82.2)	1.2 [0.5-2.9], 0.7
Self-reported psychiatric disorder	7/114 (6.1)	2/63 (3.1)	2.0 [0.4-20.5], 0.4	2/73 (2.7)	2.3 [0.4-23.4], 0.3
Immunosuppression prior to diagnosis^e	2/114 (1.8)	7/64 (10.9)	0.1 [0.01-0.8], 0.007	2/73 (2.7)	0.6 [0.05-8.9], 0.6

Unwanted sexual experiences and cervical cancer

Background	Case n=114	Older women n=64	OR [95% CI] Unadjusted p value ^a cases versus Older women ^b	Well women n=73	OR [95% CI] Unadjusted p value ^a cases versus Well women ^c
Median age onset smoking (years) (range)	15 (9-24)	17 (9-29)	p=0.04	16 (12-24)	p=0.02
Regular smoker (≥ 7 cigarettes/week for ≥ 1 year) prior to diagnosis	81 (71.1)	44 (68.7)	1.1 [0.5-2.3], 0.7	36 (49.3)	2.5 [1.3-4.9], 0.003
Regular alcohol consumption (standard drink at last once/month) prior to diagnosis	107/114 (93.9)	54/64 (84.4)	2.8 [0.9-9.2], 0.04	62/73 (84.9)	2.7 [0.9-8.7], 0.04
Non-prescription drug use at least once a month prior to diagnosis	48/114 (42.1)	17/64 (26.6)	2.0 [1.0-4.2], 0.03	12/73 (16.4)	3.7 [1.7-8.3] <0.001
Age of first sex (years)(range) (interquartile range)	16 (4-21) (15-17)	17 (10-25) (16-19)	p<0.001	17 (12-25) (16-19)	p=0.001
Median no. of heterosexual partners prior to 26 years of age	10 (4-12)	4 (2-10)	p<0.001	6 (3-10)	p=0.02
Condom use almost always (as opposed to never or almost never)	38/112 (33.9)	15/62 (24.2)	1.6 [0.3-1.0], 0.2	34/70 (48.6)	0.5 [0.3-1.7], 0.05
Sexually transmitted infection prior to diagnosis ^f	30 (26)	20 (31.3)	0.8 [0.4-1.6], 0.5	10 (13.7)	2.3 [1.0-5.5], 0.04

^ap value determined by χ^2 for categorical variables and Wilcoxon Rank-sum for continuous variables; ^bOlder women >25 years with cancer or precancer; ^cWell women ≤25

years ; ^dcervical intraepithelial neoplasia 3/adenocarcinoma in situ; ^e Any immune disease, malignancy, transplantation, history of HIV positivity, chemotherapy prior to

diagnosis, oral steroids or other immunosuppressive therapy for ≥ 1 year prior to diagnosis; ^f Sexually transmitted infection prior to presentation: previous chlamydia,

genital herpes, genital warts, or hepatitis B, C, HIV (which was not transmitted vertically, by intravenous drug use (IVDU) or transfusion), or pelvic inflammatory disease.

Table 2. Proportion of cases who had experienced unwanted sexual experiences compared to controls

	Case ^a n (%) (invasive or <i>in situ</i> disease)	CC Case ^b n (%) (invasive disease only)	Older women ^c n (%)	Well women ^d n (%)	Case versus Older women ^e Case versus Well women ^f OR [95%CI], p value ⁱ	CC case versus Older women ^g CC case versus Well women ^h OR [95%CI], p value ⁱ
Childhood sexual experiences	60/114 (52.6)	9/15 (60.0)	35/64 (54.7)	37/73 (50.7)	0.9 [0.5-1.8], 0.8 ^e 1.1 [0.6-2.0], 0.8 ^f	1.2 [0.3-4.8], 0.7 ^g 1.5 [0.4-5.5], 0.5 ^h
Childhood sexual abuse (CSA)	25/94 (26.6)	5/11 (45.5)	19/50 (38.0)	13/58 (22.4)	0.6 [0.3-1.3], 0.2 ^e 1.3 [0.5-3.0], 0.5 ^f	1.4[0.3-6.2], 0.6 ^g 2.9 [0.6-13.3], 0.1 ^h
CSA with contact	24/94 (25.5)	5/11 (45.5)	16/50 (32.0)	11/58 (19.0)	0.7 [0.3-1.7], 0.4 ^e 1.5 [0.6-3.6], 0.4 ^f	1.8 [0.4-8.1], 0.4 ^g 3.5 [0.7-16.8], 0.06 ^h
CSA with genital contact	21/94 (22.3)	5/11 (45.5)	10/50 (20.0)	8/58 (13.8)	1.2 [0.5-3.0], 0.7 ^e 1.8 [0.7-5.1], 0.2 ^f	3.3 [0.6-16.0], 0.08 ^g 5.2, [1.0-25.8], 0.01 ^h
CSA with penetrative contact	16/94 (17.0)	4/11 (36.4)	10/50 (20.0)	7/58 (12.1)	0.8 [0.3-2.2], 0.7 ^e 1.5 [0.5-4.6], 0.4 ^f	2.3[0.4-11.2], 0.2 ^g 4.1[0.7-21.7], 0.04 ^h
CSA with penile – genital contact	14/94 (14.9)	4/11 (36.4)	10/50 (20.0)	7/58 (12.1)	0.7 [0.3-1.9], 0.4 ^e 1.3 [0.4-4.0], 0.6 ^f	as above ^g as above ^h
Unwanted Adolescent Sexual Experiences (UASE)	33/114 (28.9)	7/15 (46.7)	8/64 (12.5)	18/73 (24.7)	2.9 [1.2-7.7], 0.01 ^e 1.2 [0.6-2.6], 0.5 ^f	6.1 [1.4-25.4], 0.002 ^g 2.7 [0.7-9.7], 0.09 ^h
UASE with contact	32/114 (28.1)	7/15 (46.7)	7/64 (10.9)	14/73 (19.2)	3.2 [1.3-9.0], 0.008 ^e 1.6 [0.8-3.6], 0.2 ^f	7.1 [1.6-30.7], 0.001 ^g 3.7 [0.9-13.8], 0.02 ^h
UASE with genital contact	29/114 (25.4)	7/15 (46.7)	6/64 (9.4)	12/73 (16.4)	3.2 [1.2-10.3], 0.01 ^e 1.7 [0.8-4.0], 0.1 ^f	8.5 [1.8-38.4], <0.001 ^g 4.4[1.1-16.9], 0.01 ^h
UASE with penile-genital contact	29/114 (25.4)	7/15 (46.7)	6/64 (9.4)	10/73 (13.7)	3.2 [1.2-10.3], 0.01 ^e 2.1 [0.9-4.3], 0.05 ^f	8.5 [1.8-38.4] <0.001 ^g 5.5 [1.3-21.7], 0.003 ^h
Experienced either CSA ^j or UASE ^k	44/114 (38.6)	7/15 (46.7)	22/64 (34.4)	27/73 (37.0)	1.2 [0.6-2.4], 0.6 ^e 1.1 [0.6-2.1], 0.8 ^f	2.2 [0.6-8.0], 0.2 ^g 1.9 [0.5-7.0], 0.2 ^h
Experienced both CSA ^j and UASE ^k	14/114 (12.3)	4/15 (26.7)	6/64 (9.4)	5/73 (6.9)	1.4 [0.5-4.5], 0.6 ^e 1.9 [0.6-7.1], 0.2 ^f	3.5 [0.6-17.5], 0.07 ^g 5.0 [0.8-25.5], 0.02 ^h

^a Cases with invasive or *in situ* disease; ^b Cervical cancer Case (invasive disease only diagnosed ≤ 25 years);^cWomen diagnosed with cancer or precancer >25 years of age; ^d Well women ≤ 25 years of age; ^eCases withinvasive and in situ disease versus older women; ^f Case with invasive or insitu disease versus well women; ^g

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708 Cervical cancer Case (invasive disease only) versus older women; ^h Cervical cancer Case (invasive disease
709 only) versus well women; ⁱ unadjusted p values determined by χ^2 .

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710

711 Table 3. Relationship between established risk factors for cervical cancer/dysplasia and unwanted sexual experiences

Risk factor	CSA-pos^a (n=57)	CSA-neg^b (n=145)	OR [95%CI], p value ^c	UASE-pos^d (n=59)	UASE-neg^e (n=192)	OR [95%CI] p value ^c
Regular smoking n(%)^f	48 (84.2)	82 (56.6)	4.1[1.8-10.2], <0.001	50 (84.8)	112 (58.3)	4.0 [1.8-9.7], <0.001
Median age onset smoking: years	15	16	<0.001	15	16	0.003,
Interquartile range (IQR)	(13-16)	(15-18)		(14-16)	(15-18)	
(range)	(9-29)	(9-24)		(9-24)	(9-29)	
(n)	(n=47)	(n=82)		(n=50)	(n=111)	
Duration of smoking: years (IQR)	15 (11-20)	12 (8-17)	0.03	14 (9-19)	13 (9-18)	1.0.
(range)	(1-43)	(2-39)		(4-43)	(1-39)	
(n)	(n=46)	(n=82)		(n=50)	(n=110)	
Regular alcohol consumption n(%)^g	55 (89.1)	125 (86.2)	4.4[1.0-39.9], 0.03	54 (91.5)	169 (88.0)	1.5[0.5-5.2], 0.5
Illegal drug use n(%)^h	29 (50.9)	36 (24.8)	3.1[1.6-6.3], <0.001	28 (47.5)	56 (29.2)	2.2[1.2-4.2], 0.009
Age first sexual intercourse: years	16 (14-17)	17 (16-19)	<0.001	16 (15-17)	17 (16-19)	<0.001
(IQR)	(4-25)	(14-25)		(13-22)	(4-25)	
(range)	(n=53)	(n=139)		(n=55)	(n=186)	
(n)						
No. sexual partners by 26 yearsⁱ (IQR)	9 (5-13)	6 (3-10)	0.04	10 (6-20)	6 (3-10)	<0.001
(range)	(0-60)	(1-80)		(1-60)	(0-80)_	
(n)	(n=54)	(n=138)		(n=54)	(n=185)	
History of sexually transmitted infection n(%)	27 (47.4)	32 (22.1)	3.2[1.6-6.4], <0.001	25 (42.4)	50 (26.0)	2.1[1.1-4.0], 0.02
Condom use almost always prior to 26 years (excluded never and almost never) n(%)	11/55 (20)	57/141 (40.4)	0.4[0.2-0.8], 0.007	15/58 (25.9)	72/186 (38.7)	0.6[0.3-1.1], 0.07

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712 ^a childhood sexual abuse positive ^b childhood sexual abuse negative ^c p values estimated by χ^2 for categorical variables and Wilcoxon Rank-Sum for continuous
713 variables; ^dunwanted adolescent sexual experiences positive ; ^eunwanted adolescent sexual experiences negative; ^fsmoked on average at least 7 cigarettes a week for ≥ 1
714 year; ^gConsumption of alcohol beverage at least once per month (at least one 5-oz glass of wine, 1 beer, 1 mixed drink, or 1 shot); ^huse of non-prescription drugs on a
715 regular basis (at least once per month) prior to diagnosis; ⁱ number of heterosexual sexual partners by 26 years;

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Table 4. Risk of unwanted adolescent sexual activity with penile-genital contact in cases versus controls: multivariable analysis

Logistic regression models	Cases versus older women^a	Cases versus well women^b	CC^c case versus Older women^a	CC^c case versus Well women^b
	OR [95%CI], p	OR [95%CI], p	OR [95%CI], p	OR [95%CI], p
Model 1 : adjusted for smoking , alcohol use, illegal drug use	n=178 2.2 [1.1-7.9], <u>0.03</u>	n=187 1.0 [0.7-3.6], <u>0.33</u>	n=79 22.9 [3.5-151.3], <u>0.001</u>	n=88 5.9 [1.4-24.9], <u>0.02</u>
Model 2: adjusted for AFSI ^d , no. of sexual partners ^e , almost never condom use, STI history ^f	n=174 2.4 [0.8-6.8], <u>1.0</u>	n=182 1.9 [0.7-4.5], <u>0.2</u>	n=77 11.5 [1.9-70.4], <u>0.008</u>	n=85 5.6 [1.4-22.1], <u>0.01</u>

^a Older women >25 years with cervical cancer or precancer; ^b Well women ≤ 25 years of age; ^c Cervical cancer cases ≤25 years; ^d age of first sexual intercourse; ^enumber of heterosexual partners by 26 years; ^fsexually transmitted infection;

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Figure 1 Categories of Childhood Sexual Abuse (CSA) and Unwanted Adolescent Sexual Experiences (UASE) using the Childhood Sexual Experiences Survey¹⁸ and the Sexual Experiences Survey²⁰ respectively (provided that the study definitions of CSA and UASE had been met).

721

722 Figure 1. Categories of Childhood Sexual Abuse (CSA) and Unwanted 1 Adolescent Sexual Experiences
 723 (UASE) using the Childhood Sexual Experiences Survey¹⁸ 2 and the Sexual Experiences Survey²⁰ 3
 724 respectively (provided that the study definitions of CSA and UASE had been met).

Figure 2. Recruitment of participants. *Cases with cervical cancer or precancer diagnosed ≤ 25 years; b Women >25 years with disease, c Well women ≤ 25 years

Unwanted sexual experiences and cervical cancer

Figure 3. Potential mechanisms of interaction between unwanted sexual experiences and early-onset cervical cancer

Figure 3. Potential mechanisms of interaction between unwanted sexual experiences and early-onset cervical cancer