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The burden of cervical cancer in Vietnam: Synthesis of the evidence

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ABSTRACT

There is currently no national cervical screening or HPV immunization program in Vietnam. This study aims to synthesize available data on the burden of disease and to project the burden of cervical cancer to 2049 if no major interventions are implemented. We reviewed published data sources on risk factors for HPV prevalence, high-grade lesions, cervical cancer incidence and mortality in Vietnam from 1990 to 2017. We then used the available data to project the number of new cervical cancer cases for the period 2013–2049. Data on cervical cancer incidence and mortality in Vietnam are limited; two Vietnamese cancer registries have been reported on by the International Agency for Research on Cancer, which cover urban populations representing ~20% of the national population. The reported age-standardized cervical cancer incidence in Hanoi was 6.7 (1993–1997), compared to 28.8 and 14.1 per 100,000 women in Ho Chi Minh City (1995–1998 and 2009–2012, respectively). Cancer mortality data are not uniformly available from cancer registries or mortality surveys in Vietnam because cause of death has not been routinely ascertained. Based on available urban population registry data, estimated rates in the rural population, and forward projection of existing trends, we estimate that without any further intervention, the number of new cases will increase from 6930 (range 5671–8493) in 2012 to 8562 (range 5775–12,762) in 2049, giving a total of 379,617 (range 276,879–542,941) new cases over the period 2013–2049. These findings help underpin the case for the delivery of HPV vaccination and cervical screening in Vietnam, and support similar initiatives in other low- and middle-income countries.

1. Introduction

Cervical cancer has been previously estimated to be the fourth most common cancer and the fourth most common cause of cancer death for women worldwide in 2012, with an estimated 528,000 new cases and 266,000 deaths annually [1]. In Vietnam, prior estimates suggest it was the fourth most common cancer in women with 5146 new cases and 2423 cervical cancer deaths in 2012 [1]. Several pilot cervical screening projects have been conducted to evaluate different cervical screening strategies over the last few decades, including use of cytology and visual inspection with acetic acid (VIA). However, cervical screening in Vietnam is currently opportunistic, and findings from a survey in 2003 showed that approximately 4–6% of women across urban and rural regions have been screened [2]. In 2011, the Vietnam Ministry of Health (MOH) issued guidelines for screening, diagnosis and treatment of precancerous lesions as secondary prevention for cervical cancer, in which various screening techniques including VIA, cytology and HPV DNA testing were recommended [3]. The guidelines recommended cervical screening with cytology and VIA tests for women aged 21–70 years, with particular focus on those 30–50 years. A 2-yearly screening frequency is recommended, extending to every three years for women with three consecutive negative tests. Based on these guidelines, several provinces in Vietnam have been using VIA as a cervical screening test [4], however, a national organized cervical screening program has not yet been established.

Although human papillomavirus (HPV) vaccination has been shown

Abbreviations: HPV, human papillomavirus; IARC, International Agency for Research on Cancer; CI5, cancer incidence in five continents; ASR, age-standardized rate

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to effectively prevent cervical precancer, the vaccine has not yet been introduced into the Vietnamese national immunization program. A demonstration project was conducted in four districts of two provinces in 2008–2010 for approximately 7000 pre-adolescent girls (aged 11–13 years) to assess the acceptability, feasibility, and delivery cost of the vaccine [5,6]. While this pilot project showed a high level of acceptability and coverage (96.1% of the targeted population achieved) [5], the additional costs of delivering a new vaccine to a new population group (i.e. to pre-adolescents rather than young children) poses a challenge [7]. Unfortunately, from 2017, Vietnam is no longer eligible for support from Gavi, the Vaccine Alliance, and the national government faces competing demands for funding for early childhood vaccines [8].

HPV has been identified as the necessary cause of virtually all cervical cancers [9,10]. HPV DNA is found in virtually all invasive squamous cervical cancers in well-controlled studies [11,12]. In addition, studies designed to detect prevalent histologically-confirmed cervical intraepithelial neoplasia, grades 2 or 3 (CIN2/3), alternatively referred to as 'HSIL' (high-grade squamous intraepithelial lesions), provide an important indicator of the prevalence of high-grade precursor lesions that precede the development of invasive cervical cancer [13]. Therefore, in unscreened populations study-ascertained prevalence of HPV infection and HSIL can be considered to be surrogate markers for the cervical cancer burden [14]. There are also factors which are likely to be associated with the transmission of HPV (correlates of HPV infection) and the progression of HPV infection to cervical cancer (cofactors for HPV progression), which are also important to consider when examining the likely patterns of cervical cancer in a population. International pooled analyses have identified the correlates of HPV infection as: age at first sexual intercourse, number of lifetime sex partners, and any STI exposure [15,16], and that oral contraceptive use, smoking, parity, and age at first full term pregnancy are cofactors for cervical cancer development [17–19].

In order to better understand the future burden of disease and thus inform the potential impact of future cervical cancer prevention initiatives in Vietnam, we reviewed the literature and synthesised evidence on the disease burden (cervical cancer incidence, mortality, HPV and HSIL prevalence) and risk factors for cervical cancer (correlates of HPV infection and co-factors for HPV progression), to project the number of new cervical cancer cases in Vietnam for the period 2013–2049 in the absence of the implementation of any intervention.

2. Materials and Methods

2.1. Evidence on the burden of cervical cancer and risk factors for the disease

2.1.1. Prevalence of HPV infection and high-grade squamous intraepithelial lesions (HSIL) in the general female population

We systematically reviewed all available publications on the prevalence of HPV infection and/or histologically-confirmed HSIL reported in the general Vietnamese female population from 1990 to 2017. MEDLINE, MEDLINE-in process, Embase and Global Health databases were searched using text terms, and where available, using database-specific subject headings. Reference lists of all relevant articles were checked for potential additional articles. We also searched other sources, including Vietnamese language journals. Details of inclusion and exclusion criteria and a complete list of search terms used for all search strategies are included as Tables A1 and A2 in Appendix A. Random-effect meta-analyses were used to synthesise the prevalence of HPV infection (any HPV and high-risk oncogenic HPV) [9,20].

2.1.2. Correlates and cofactors of HPV infection

Using the same databases and similar search strategies as above, we systematically searched for all available publications from 1990 to 2017 that reported on the correlates of HPV infection or cofactors for progression to cervical cancer in Vietnamese women. Details of inclusion and exclusion criteria and a complete list of search terms used for all search strategies are included as Appendix Tables B1–B4 in Appendix B.

2.1.3. Cervical cancer incidence

We reviewed all available data up to 2017 from the Vietnamese cancer registries as reported in the Cancer Incidence on Five Continents (CIV) by the International Agency for Research on Cancer (IARC), and as reported to the Vietnam National Cancer Institute (Vietnam NCI). We examined data on cervical cancer incidence in Hanoi and Ho Chi Minh City (HCMC) as reported in IARC's CIV, Volume VII (which included data reported by the Hanoi cancer registry 1991–1993), Volume VIII (which included data reported by the Hanoi cancer registry 1993–1997 and the HCMC cancer registry 1995–1998), and Volume XI (which included data reported by the HCMC cancer registry 2009–2012) [21–23]. We also reviewed cervical cancer incidence rates from other non IARC-reported cancer registries, including Hanoi, HCMC, Thai Nguyen, Hai Phong, Hue and Can Tho, which were reported to the Vietnam NCI for the periods 2001–2004 and 2004–2008 (Appendix C, Table C1). It has been suggested that there is an association between socio-economic status and cancer in general, and cervical cancer in particular [24,25]. We therefore extracted data on the Vietnamese regional and national gross domestic product per capita (GDPpc) from the Government Statistics Office (GSO) website to measure a ratio of each site's GDPpc to the national average GDPpc as a proxy comparator for the socio-economic status of populations covered by the different cancer registry sites (Appendix C, Table C2).

2.1.4. Cervical cancer mortality

We reviewed all available published mortality surveys conducted in Vietnam up to the end of 2017 and also reviewed the most recent cervical cancer mortality rates as estimated in GLOBOCAN 2012 [1]. We also reviewed cervical cancer mortality data estimated for Vietnam in the World Health Organization (WHO) mortality database [26].

2.2. Estimated number of cervical cancer cases for 1999, 2009 and projection of a feasible estimated range of newly diagnosed cervical cancer cases in Vietnam for the period 2013–2049

Our initial review of cervical cancer incidence showed a substantial variation between northern urban (Hanoi data) and southern urban (HCMC data) areas of Vietnam. Additionally, given that cervical cancer incidence data have not been reported for rural regions, where approximately 70% of the total population lives and where cervical screening is probably less available, it is likely that the incidence of cervical cancer amongst a substantial proportion of Vietnamese women would be even higher [27]. Therefore, to account for this variation in disease epidemiology and demographics across these regions, we defined three geographic regions – northern urban, southern urban and rural regions in our projections. For the current and past rates, we assumed that the rural, northern urban, and southern urban regions of Vietnam accounted for approximately 70%, 15%, and 15% of the total population, similar to assumptions used in GLOBOCAN2012 [1].

We used population data as estimated from the 1999 and 2009 national population censuses for the estimate of new cervical cancer cases in 1999 and 2009 [27,28]. We used the available IARC-certified age-specific cervical cancer incidence rates from the Hanoi cancer registry (1993–1997) and from the HCMC cancer registry (1995–1998) to inform assumptions for cervical cancer incidence rates for the northern urban and southern urban regions respectively [22], and the average of age-specific cervical cancer incidence from IARC-certified registries (1998-2002) covering unscreened populations in less-developed countries (which we estimated as ASR = 20.2 per 100.000 women using data from IARC's CIV-IX) was applied for the rural regions [29].

We used two approaches to estimate future cancer cases from 2013

onward. The first detailed regionally-stratified (here after termed 'detailed') approach the assumptions of cervical cancer incidence rates by regions as described above, except we used the new IARC-certified HCMC cancer registry data (2009–2012) for the cervical cancer incidence rates for the southern urban region [23]. The second simplified national level (here after termed 'simplified') approach, extrapolated forward using as a basis the age-specific cervical cancer rates estimated for Vietnam by GLOBOCAN 2012 [1]. For both projection methods, we used the regional-projected population data based on the 2009 population census survey (for year 2013) and the 2014 Vietnam intercensal population survey (for years 2014-2049),using the medium fertility level [30,31].

In order to account for trends in cervical cancer incidence rates over time, for both detailed and simplified approaches, we utilised previous estimates that in medium human development index (medium HDI) countries, cervical cancer incidence would reduce by 1.8% each year up to 2030 as result of a decrease in fertility rates and an improvement in socioeconomic conditions (and perhaps some opportunistic screening) [32,33]. Vietnam was classified as a medium HDI in 1995. Therefore, for the detailed approach we applied a 1.8% reduction annually in cervical cancer incidence from 1999 (using the 1999 estimated population), 2009 (using the 2009 estimated population) and 2013 to 2030 (using the projected population), and for the simplified approach we applied this reduction from 2013 to 2030 (as the simplified projection used the cervical cancer incidence rates estimated by GLOBOCAN in 2012). For the period 2031–2049, we assumed the cervical cancer rate will remain stable at the same rate as in 2030 in both detailed and simplified projections. This was based on the assumption that although the decrease in cervical cancer incidence rates may be related to increasing access to better health services, better education, and changes in HPV exposures, this would not continue indefinitely. The total number of projected new cervical cancer cases for the whole country was the weighted sum of the projected new cervical cancer cases of the three regions. The projection assumptions are summarized in Appendix D, Table D1.

In the absence of organised national cervical screening and HPV vaccination programs, and based on the evidence of our review of risk factors, we assumed that there would be no detectable further impact from the existing interventions over the period 2013–2049, given that cervical screening occurs only opportunistically and in the context of our assumption (above) that rates will decrease by 1.8% per annum in base case projection [15,17–19,34]. However, a best case scenario of 3.6% reduction in cervical cancer incidence annually up to 2030 and a worst case scenario of no ongoing reduction in incidence was performed to estimate a range of outcomes for both approaches. Additionally, given there are no available data for cervical cancer incidence for rural areas of Vietnam, a sensitivity analysis using a low cancer incidence rate for rural areas (similar to the incidence of Hanoi [ASR = 6.8/100,000 women]) was performed to take into account the uncertainty of the disease burden in rural areas of Vietnam. Similarly, given the substantial reduction of cervical cancer incidence rates in HCMC over the period 1995–2012, a sensitivity analysis applying the higher cervical cancer incidence of HCMC was also conducted. These two sensitivity analyses were applied for detailed projections only.

3. Results

3.1. Evidence on the burden of cervical cancer and risk factors for the disease

3.1.1. The prevalence of cervical HPV infection and high squamous intraepithelial lesions (HSIL) in the general female population

We identified 115 citations from the literature search, 10 articles (Vietnamese language) and 1 PhD thesis from other sources. After screening for titles and abstracts, 30 full text papers in English, 7 full text papers in Vietnamese and 2 PhD theses (1 in Vietnamese) were retrieved and assessed for inclusion and exclusion criteria. Of these, 8 articles and one PhD thesis reporting on 5 primary HPV prevalence surveys (5 articles were reported from one primary survey) were eligible for the HPV prevalence review, and 7 articles and one PhD thesis, all in Vietnamese, were included in the HSIL prevalence review (a flow diagram of the study selection process is shown in Appendix A, Fig. A1).

During the period 1990–2017, there were 4 HPV population-based surveys conducted across different cities/provinces in Vietnam, including Hanoi (reported in 3 surveys), HCMC (reported in 3 surveys), Can Tho (reported in 1 survey), Hue (reported in 1 survey), and Da Nang (reported in 1 survey) [35,36] (A summary of the included studies is presented in Appendix E, Table E1). All surveys were conducted in urban or semi-urban populations. Population samples varied in terms of sample sizes (approximately 400–1550 women/site). In all surveys, sexually active women completed interviews for socio-demographic and lifestyle information and then received a gynaecological examination. Samples of exfoliated cervical cells were collected by heath staff during pelvic examination for cytology and HPV testing. All studies utilised PCR testing although different technologies were used, including HPV GP5+/6+ primer-mediated PCR enzyme immunoassay (EIA), HPV MY09/11 primer-mediated PCR EIA, real time PCR genotype Reverse Dot Blot (RDB) kit, and real-time PCR using 14 HPV Genotypes Real-TM Quant Kit [35–40].

Meta-analysis was employed to synthesize the HPV prevalence results from these studies. Individual and pooled estimates of any HPV and high-risk HPV prevalence with 95% confidence intervals and stratified by north, south and central urban regions are shown in Fig. 1. The overall pooled prevalence of any HPV and high-risk HPV from all studies was 8% (95% CI: 6%–11%) and 6% (95% CI: 4%–8%), respectively, with heterogeneity being significant in both (p[het] = 0.001). Similar prevalence for any HPV was observed by region: 7% (95% CI: 3%–11%) for Northern Urban, 10% (95% CI: 9%–11%) for Southern Urban, and 9% (95% CI: 7%–11%) for Central Urban (p[het] = 0.14; however, Some differences in prevalence were observed for high-risk HPV. The estimate of high-risk HPV prevalence was 3% (95% CI: 2%–5%) for Northern urban, 8.0% (95% CI: 6.0%–10.0%) for Southern Urban and 6% (95% CI: 5%–8%) for Central Urban, p[het] = 0.01 (Fig. 1). Significant intra-region-group heterogeneity (p[het] = 0.001) was found in almost all stratified regions for both any HPV and high-risk HPV prevalence (except the southern urban where any HPV prevalence was homogenous, p[het] = 0.17). Additional findings of the review of HPV prevalence are reported in Appendix E.

The prevalence of HSIL was reported in several cytology screening studies. Six pilot cervical cytology screening projects were conducted across different cities/provinces in 1992–2011 (Table 1). Nguyen Vuong et al., 2000 reported results of a pilot cytological screening study supported by the government for 26,270 women in 216 communities across northern, central, and southern regions of Vietnam during 1992–1999. Women were included if they were sexually active and aged 20–50 or older. Overall, the prevalence of HSIL was reported to be 0.85% (95% CI: 0.75%–0.98%, $n_{HSIL/screened}$ = 225/26,270) [41]; HSIL prevalence was 0.95% (95% CI: 0.66%–1.33%, $n_{HSIL/screened}$ = 34/3568) in Hanoi, and 0.97% (95% CI: 0.57%–1.61%, $n_{HSIL/screened}$ = 16/1608) in Can Tho [42]. The second pilot cervical cytological screening study was supported by the government for the national cancer prevention and control program in 2008–2010 [43]. A total of 70,505 sexual active women aged 35–60 in 140 communities of 7 cities/provinces across northern, central and southern regions of Vietnam were screened with cytology tests [44]. Overall, HSIL prevalence was 1.29% (95% CI: 1.21%–1.38%). Another pilot community-based cytological screening study was conducted in 17,272 sexual active women aged 30–55 in Hue province (central region) during 1999–2009 [45]. The

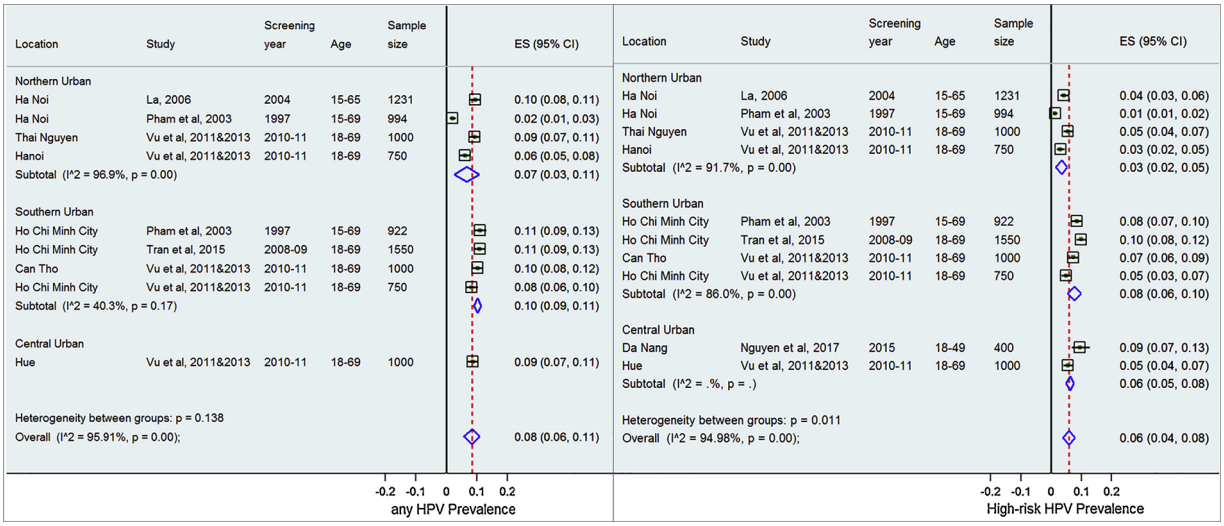


Fig. 1. Meta-analysis of the prevalence of any HPV infection and high-risk HPV infection among sexually active women in northern urban, southern urban and central urban regions of Vietnam.
Note: ES (95%CI): Estimate (95% Confidence Interval); HPV: Human Papillomavirus.

estimated prevalence of HSIL was 0.38% (95% CI: 0.29%–0.48%) ($n_{HSIL/screened}$ = 65/17,272). Several small cervical cytological screening studies (sample size: 1000–3500) were also conducted in women at various age ranges during 2008–2013 in different cities/provinces [46–49]. We did not have sufficient detailed reported data from the primary studies to pool data on HSIL prevalence to conduct meta-analysis. Overall, the reported prevalence of HSIL ranged from 0.1% to 2.1% in the various surveys and studies (Table 1). When considering only in the four large screening projects conducted from 1999 to 2010, the estimated prevalence of HSIL in women aged 35–60 years ranged from 0.38% to 1.29%.

3.1.2. Population exposure to correlates of high-risk HPV infection and cofactors of progression to cervical cancer

Our search identified 93 articles which could potentially provide information on the correlates of HPV infection and the cofactors for cervical cancer in the general population, and 2 articles and 2 reports from Vietnamese national youth surveys were identified. After screening for titles and abstracts, a total of 24 publications that potentially provided relevant information were retrieved and assessed for inclusion and exclusion criteria. Seven papers and 2 reports that reported on the risk factors or determinants of HPV infection and cervical cancer among the general population in Vietnam were included. The main reasons for excluding articles were: ineligible study populations (HIV positive women or sex workers) and non-specified study outcomes. A flow diagram of the study selection process is shown in Appendix Fig. B1.

The previously identified studies of HPV prevalence in Vietnam published in 1990–2017 were found to have also report on the risk factors for high-risk HPV infections. Early age at first sexual intercourse, lifetime number of sex partners, and STI exposure (HSV-2) were found to be associated with high-risk HPV infections, with odds ratios ranging from 4.2 to 4.7, 3.8 to 4.8 and 2.4 to 4.9, respectively (Table 2) [35,38,39].

Surveys indicated that there have been changes in sexual behaviours in the general Vietnamese population over time and between regions. Ghuman et al. conducted a survey to identify changes in premarital sexual behaviour among men and women aged 24–56 years who were married in 3 different periods (1963–1971, 1977–1985, and 1992–2000) in Red River Delta (northern region) and Ho Chi Minh City and its surrounding areas (southern region) [53]. The study found that premarital sex was more common among married people in a younger cohort (1992–2000) than older cohorts (1963–1971, 1977–1985) in both sexes. Additionally, while premarital sex seems to be equally reported in northern and southern regions in married people in a younger cohort (31% in men and 8%–12% in women), this proportion was higher for older cohorts in the south [53]. The trend towards changing sexual behaviours in younger generations was also identified from the results of two rounds of the national youth survey (SAVY I and SAVY II) which interviewed 7000–10,000 males and females aged 14–25 years across Vietnam using a self-administrated questionnaire in 2003 and 2009, respectively [51,52]. Although less than 10% of the young respondents reported on their premarital sexual experience, the increasing percentage of young respondents reporting premarital sex (9.5% vs.7.6%) over the two surveys implied that young people had an increasingly open attitude to their sexual lives compared to older generations. The surveys also suggested that age at sexual debut has become younger over time, with the mean age at first sexual intercourse reported as 18.0 and 18.2 years for females and males respectively in the 2009 survey, compared to 19.4 and 20 years in the 2003 survey. The trend towards earlier initiation of sexual intercourse occurred in both urban and rural areas [51,52].

Regarding the level of exposure of the general population to cofactors for cervical cancer progression, the evidence is relatively limited. Vietnam is regarded as having successfully implemented a family planning program, which has led to a substantial reduction in the total fertility rate (TFR), from 6.1 births per woman in the period 1969–1974 to 2.1 births per woman in 2015 [55,56]. In the period 2004–2015, although the most popular contraceptive method in Vietnam is the use of an Intra-Uterine Device (IUD) (47.9–55.9%), there has been an increase in the prevalence of oral contraceptive pill usage, which is the second most common contraceptive method, increasing from 11.9%

Table 1
Summary of reported survey findings for HSIL prevalence among the general female population in Vietnam.

Authors	Study period	Study location	Number of screened women	Screening age	HSIL prevalence (%)
Trinh Quang Dien et al., 2014 [46]	Not reported	Ha Nam	3,693	30-59	0.11% (95%CI: 0.03%-0.28%)*
Le Quang Vinh & Luu Thi Hong, 2013 [47]	2011	Thai Nguyen	1,004	20-60	1.89% (95%CI: 1.14%-2.94%)*
Le Quang Vinh, 2012 [48]	2011	Hue	1,000	20-60	1.90% (95%CI: 1.15%-2.95%)
		Can Tho	1,001	20-60	2.09% (95%CI: 1.30%-3.18%)*
Nguyen Tuan Hung & Tran Van Thuan, 2012 [43]	2008-2010	140 communes of 7 cities/provinces across Vietnam	70,505	35-60	1.29 (95%CI: 1.21%-1.38%)*
Tran Thi Loi et al., 2010 [49]	2008-2009	HCMC	1,550	18-69	0.52% (95%CI: 0.22%-1.01%)
Tran Dang Khoa et al., 2008 [50]	2005-2007	Hanoi	10,140	35-60	0.64% (95%CI:0.50-0.82%)*
Nguyen, Van Bang et al., 2009 [45]	1999-2009	Hue	17,272	30-55	0.38% (95%CI: 0.29%-0.48%)*
Trinh Quang Dien et al., 1995 [42]	1992-1994	Hanoi	3,568	18-77	0.95% (95%CI: 0.66%-1.33%)*
		Can Tho	1,608	18-77	0.97% (95%CI: 0.57%-1.61%0*
Nguyen Vuong et al., 2000 [41]	1992- 1999	216 communes and 5 hospitals across Vietnam	26,270		0.85% (95%CI: 0.75%-0.98%)*
Pham et al., 2003 [35]	1997	Hanoi	994	18-65	0.1% (95%CI: 0.003%-0.6%)*
		HCMC	922	18-65	0.8% (95%CI: 0.3%-1.6%)*

Note: (*) 95% confidence interval was calculated from frequencies reported by authors; NA: not available

(2004) to 18.8% (2015) [56]. The successful family planning program and the two-child policy in Vietnam also led to a reduction in the number of children per woman, with the percentage of women having a third or higher order birth decreasing from 20.8% in 2005 to 14.2% in 2012 [56]. Smoking is generally uncommon in Vietnamese women, with the prevalence of ever smoking being reported as only 2.6%–3.6% [57,58]. The prevalence of tobacco smoking has been shown to have decreased in both sexes [57].

Findings from HPV prevalence surveys in Vietnam revealed some evidence of an association between HPV infection and oral contraceptive use, nulliparity and smoking (Table 2) [35,38,39]. An association with oral contraceptive use was only reported in the IARC's 1997 HPV survey, with a reported OR of 2.9 (95% CI: 1.1–7.2) in HPV-positive vs. negative groups in HCM city [35]. In the same study, nulliparity was identified as being significantly associated with HPV infection in Hanoi - OR: 6.0 (95% CI: 1.1–34.0) and HCM city – OR: 3.0 (95% CI: 1.6–5.6) [35]. Smoking was reported associated with HPV infection in both the 1997 and 2008–09 HPV surveys, with ORs ranging from 2.8 (95% CI: 1.0–8.2) [35] to 24.2 (95% CI: 3.3–180.2), [38] respectively. Although multivariate models were used to generate the odd ratios to adjust for potential confounding (women's age, education etc.), small sample sizes in the original studies may limit the generalizability of these findings.

3.1.3. Recent estimates of cervical cancer incidence

Only two cancer registries in Vietnam (Hanoi and HCMC) have ever been used for reporting by IARC (Fig. 2). Data from the Hanoi registry were reported in two of IARC's CIV volumes (VII and VIII), for the periods 1991–1993 and 1993–1997 [21,22]. HCMC data was reported in two volumes, for the period 1995–1998 and 2009–2012 [22,23]. While both registries are located in urban areas, the IARC-reported data showed that there was substantial variation in cervical cancer incidence between these two regions. Cervical cancer incidence rates in Hanoi ranged from 6.1 to 6.7 per 100.000 women (standardized to the world standard population, ASR-W) [21,22]. By comparison, the incidence rate in HCMC was higher at 28.8 per 100.000 women in the period 1995–1998 and 14.1 per 100,000 women for the period 2009–2012 [22,23]. This is a remarkable apparent decrease in the cervical cancer incidence in HCMC over the last twenty years (1995–2012) given the lack of organized, widespread cervical screening; it is possible that over-reporting issues and some cohort effects in the earlier period (HCMC cancer registry data in the period 1995–1998) might play a partial role in this reported decrease (HCMC cancer registry data in the period 2009–2012). (see Discussion section).

The data from these two registries are unlikely to be representative of the entire Vietnamese population. The female populations covered by the Hanoi and HCMC registries accounted for only 7.0% and 13.3%, respectively, of the total female population in Vietnam in 1994 and thus only 20% of the national population was covered by these registries [28]. Furthermore, the GDPpc of both Hanoi and HCMC is higher than the Vietnamese national average GDPpc; the ratio of GDP per capita in these two cities to the national average ranged from 1.5 to 1.8 (Hanoi) and 2.1 to 2.5 (HCM city) over the period 2001–2013 (Appendix C, Table C2) [60].

From 2000 onwards, besides the Hanoi and HCMC cancer registries, another four cancer registries have been operating in Vietnam – Thai Nguyen, Hai Phong, Hue, and Can Tho. The data from these registries were reported to the Vietnam NCI, but they have not ever been reported by IARC (Appendix C, Table C1) [61,62]. In 2001–2004 and 2004–2008 the reported cervical cancer incidence rates ranged from 3.5 to 5.5 per 100,000 women in Thai Nguyen, Hai Phong, and Hue [61,62]. These are provinces with lower GDPpc and a higher proportion of rural residents (Appendix C, Table C2) [27]. The incidence rates reported for the higher GDP and less rural areas (Hanoi, HCMC and Can Tho) were much higher, ranging from 9.5 to 20.8 per 100,000 women, respectively [61,62]. Additionally, the data of non-IARC reported cancer

Table 2
Current available evidence on correlates and cofactors of high-risk HPV infection in Vietnam.

Study	Authors, published year	Study location	Sample population	Age	Sample size	Correlates			Cofactors		
						Age at first sexual intercourse OR (95%CI)	≥ 2 vs. 1 lifetime sex partners OR (95%CI)	Ever HSV-2 infection vs. never OR (95%CI)	ever smoked vs never smoking OR (95%CI)	Current oral contraceptive use vs. never OR (95%CI)	Parity OR (95%CI)
HPV prevalence survey, 1997 (supported by IARC)	Pham et al., 2003 [35]	Hanoi HCM city	Asymptomatic sexual active women	*15-69*	1916	NA	4.8 (1.9-12.3)*	2.4 (1.5-3.9)	3.0(0.9-10.2)	4.0 (1.9-9.7)	4.5(2.2-9.0)#
HPV prevalence survey, 2004	La Hanh, 2004 (PhD thesis) [37]	Hanoi	Asymptomatic sexual active women	*15-69*	*1231*	NA	NA	4.92 (1.49-16.18)	NA	NA	NA
HPV prevalence survey, 2008-2009	Tran et al., 2015 [38]	HCM city	Asymptomatic sexual active women	18-69	750	4.69 (1.83-12.03), P = 0.006**	NA	NA	24.24 (3.26-180.24), p = 0.002	NA	NA
HPV prevalence survey, 2010-2011	Vu et al., 2011 [39]	Hanoi, HCM city	Asymptomatic sexual active women	18-69	1500	4.20 (1.77-9.96), p < 0.001	3.83 (1.88-7.83), p < 0.001	NA	NA	NA	NA
Youth survey 2003 (SAVY 1)	Vietnam Ministry of Health, 2005 [51]	63 provinces	Youth	14-25	10,044	Male: 20; Female: 19.4	NA	NA	NA	NA	NA
Youth survey 2009 (SAVY 2)	Vietnam Ministry of Health, 2010 [52]	63 provinces	Youth	14-25	7,584	Male: 18.2; Female: 18	NA	NA	NA	NA	NA
Continuity and change in premarital sexual behaviour in Vietnam, 2003-2004	Ghuman et al., 2005 [53]	14 provinces in North and South	Married men/women at different marriage cohorts 1963-1975 1977-1985 1992-2000	24-56 years	2,592	NA	more common in younger marriage cohorts (1990-2000) than in older cohorts (1963-1971, 1977-1985); and more common in the South vs. North;	NA	NA	NA	NA
Attitudes about sex and marital sexual behaviour in Hai Duong Province, Vietnam	Ghuman et al., 2005 [54]	Hai Duong (North)	Married men/women at different marriage cohorts 1965-1975 1976-1985 1986-1992 1993-2000	24-56 years	800	NA	more common in younger marriage cohorts	NA	NA	NA	NA

(*) > 3 lifetime sex partner vs. 1 lifetime sex partner; (**) age > 26 vs. < 20 ; (#) nullparity vs. 1-2 children;

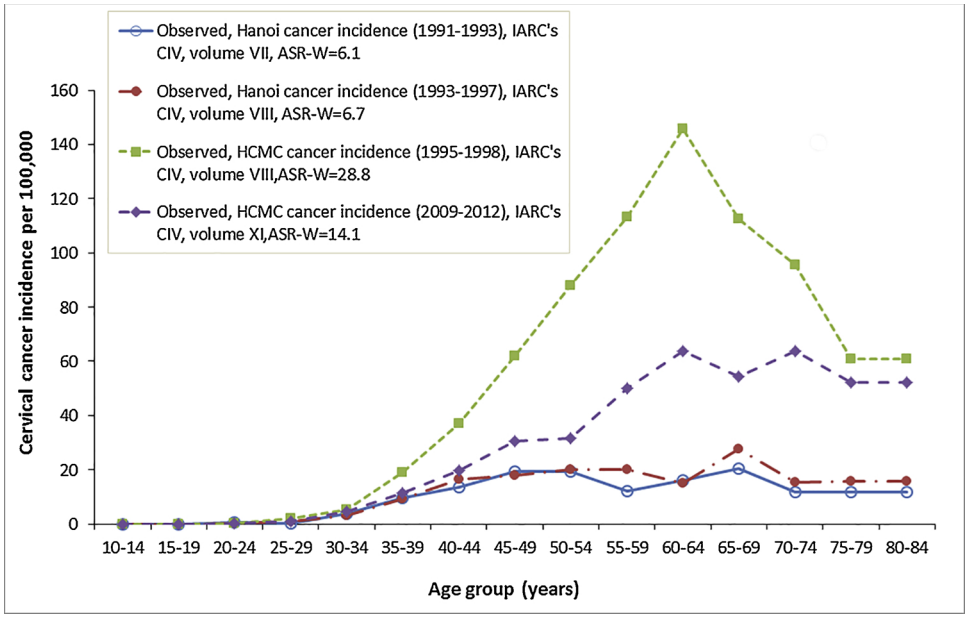


Fig. 2. Age-specific incidence of cervical cancer in Vietnam from IARC-certified cancer registries.
Data sources: Parkin et al., 1997 [21]; Parkin et al., 2002 [22], Bray et al., 2017 [23]. ASR-W: Age-standardized rate by world population; HCMC: Ho Chi Minh City; IARC: The International Agency of Research on Cancer; CIV: Cancer Incidence in Five Continents.

registries during 2000–2008 were also consistent with those shown by the IARC-reported data in the 1990s in that the incidence of cervical cancer in the southern provinces/cities (HCMC, Can Tho) is generally higher than the incidence reported in the northern provinces (Hanoi, Hai Phong, Thai Nguyen).

3.1.4. Estimates of cervical cancer mortality

Several mortality surveys were conducted in Vietnam over the period 1999–2014 (Table 3), but only one survey reported the rate of female genital cancer mortality, which would include cervical cancer. The largest cancer mortality survey was conducted in 2005–2006 and reported patterns of cancer mortality by location [63]. The survey was based on data collected from the community-based mortality registration system in all 64 provinces of Vietnam, and covered more than 90% of the national population [63]. This mortality registration system was established nationally in 1992 by the Ministry of Health (MOH). The system uses a registration book, the "A6 mortality registration book", which is recorded by health staff at every commune health centre in Vietnam [64]. Findings from the 2005–2006 survey indicated that cervical cancer and other female genital cancers caused 9.1% of the total number of cancer deaths in females during that period, indicating that the cervical cancer deaths would probably have accounted for less than 9% of the total female cancer deaths. This finding is similar to the GLOBOCAN 2012 estimate for Vietnam, in which the total crude death rate of cervical cancer and other female genital cancers was estimated at 9.2% of the total number of deaths from all female cancers [1]. However, both these estimates of the cervical cancer mortality rate are lower than the GLOBOCAN 2012 estimate of the cervical cancer mortality rate for less-developed countries, which was 12.6% of the total female cancer deaths. This might suggest some underestimation and/or misclassification in the deaths caused by cervical cancer, given the community-based mortality registration system in Vietnam.

One other potential source of information on cervical cancer mortality rates in Vietnam is a 2010 study which used data from the 2007 population change survey (PCS) which covered 2% of the national population. The study used identified death cases reported to the 2007 PCS by households during 1st April 2006 to 31st March 2007 to classify cause of death via retrospective interviews with the deceased's relatives for 6798 reported deaths [65]. The leading cause-specific mortality rates for males and females were classified using ICD-10, however cervical cancer mortality rates were not reported on the list. Nonetheless, this study did report that "other cancer of the uterus" accounted for about 3% of the total leading mortality causes in females [65]. If cervical cancer was categorized under the category of "other cancer of the uterus", this result suggests an underestimation and/or misclassification in the reporting of the mortality rates of cervical and other cancers in the 2007 PCS. Two other mortality surveys were conducted in 2008–2009 (conducted in 16 out of 63 provinces/cities, a sample of 3% of the national population) and 2014 (conducted in 2 out of 63 provinces/cities) to verify the causes of deaths which were identified from the currently available mortality registration systems [66,67]. However, data on cervical cancer mortality were not reported in either study.

3.2. Estimated number of cervical cancer cases in Vietnam for 1999–2009 and predicted cases for 2013–2049

Fig. 3A shows the estimated number of cervical cancer cases for 1999–2009 and the projected number of cases for 2013–2019 under the simplified and detailed assumptions for cancer incidence rates (main projection), in the absence of any further interventions. It is estimated that in 1999 the number of new cervical cancer cases diagnosed in Vietnam was 5957 (range 5848–6066), and in 2009 was 6436 (range 5480–7560). For 2012 our projections predicted a total of 5228 new cervical cancer cases using the simplified approach, and 6930 (range 5671–8493) new cases using the detailed approach. By 2050 we estimate a 16% (2%–33%) increase in the number of new cervical cancer cases using the detailed approach, resulting in a total of 8562 (range 5775–12,762) new cases. In comparison the simplified approach predicted an increase (or decrease) of 17% (-6% to +34%), leading to a total of 6,295 (range 4949–7971) new cases in 2049. Over the entire projection period (2013–2019) a total cumulative number of 379,617 (range 267,879–542,941) or 281,911 (range 237,934–335,809) cervical cancers will be diagnosed based on the detailed or simplified projection methods, respectively.

A sensitivity analysis using a lower assumption for cervical cancer incidence rates for rural regions (ASR = 6.8/100,000 women – similar to Hanoi cervical cancer incidence) – resulted in 45% (range 43%–47%) fewer cumulative numbers new cancer cases (209,032 [range 153,646–287,786]) by 2050 (Fig. 3B). In contrast, if the higher cervical cancer incidence in HCMC reported in 1995–1998 was assumed for the southern urban population, by 2050 a total cumulative number of

Table 3
Summary of mortality surveys in Vietnam.

Mortality Survey	Reported by	Survey period	Selected provinces/ cities	% total Vietnamese population covered	Data source	Cervical cancer & other female genital cancer/ total female cancer deaths	Crude/adjusted mortality rate of cervical cancer
Survey 1	Le et al., 2007 [63]	2005-2006	64/64	92.3%	A6* at CHC**	9.13% #	NA
Survey 2	Le et al., 2006 [68]	1999-2005	3/64	5.4%	A6* at CHC**	NA	NA
Survey 3	Le et al., 2012 [69]	2005-2010	1/63	3%	A6* at CHC**	NA	NA
Survey 4	Ngo et al., 2010 [65]	2007-2008	64/64	3%	Retrospective interviews to verify the cause of death	NA	NA
Survey 5	Nguyen et al., 2012 [67]	2008-2009	16/63	3%	Retrospective interviews to verify the cause of death and the completeness and reliability of mortality data	NA	NA
Survey 6	Tran et al., 2018 [66]	2014	2/63	NA	Retrospective interviews to verify the cause of death and the completeness and reliability of mortality data	NA	NA
	GLOBOCAN 2012 [1]	2012			Estimated	9.2%##	5.3%
	GLOBOCAN 2012 [1]	2012		LDC***	Estimated	12.6%	8.1%

Note: (*) A6: Death registration book; (**) CHC: Commune Health Centre; (***) LDC: Less Developed Countries; NA: Not available (#) and (##) Data from these two sources are possibly interdependent as it is noted in the methodology by GLOBOCAN 2012 that they used cancer mortality data from a country report of cancer incidence, survival and mortality, 2005-2006 by Le Tran Ngoan [70]. Data source: Le et al, 2006 [68]; Le et al, 2007 [63]; Ngo et al, 2010 [65]; Le et al, 2012 [59]; Nguyen et al, 2012 [67]; Ferlay et al, 2012 [1].

431,207 (range 285,479–651,398) women would be diagnosed with cervical cancer using the detailed projection method, an increase of 14% (range 7%–20%) compared to the main projection results (Fig. 3C).

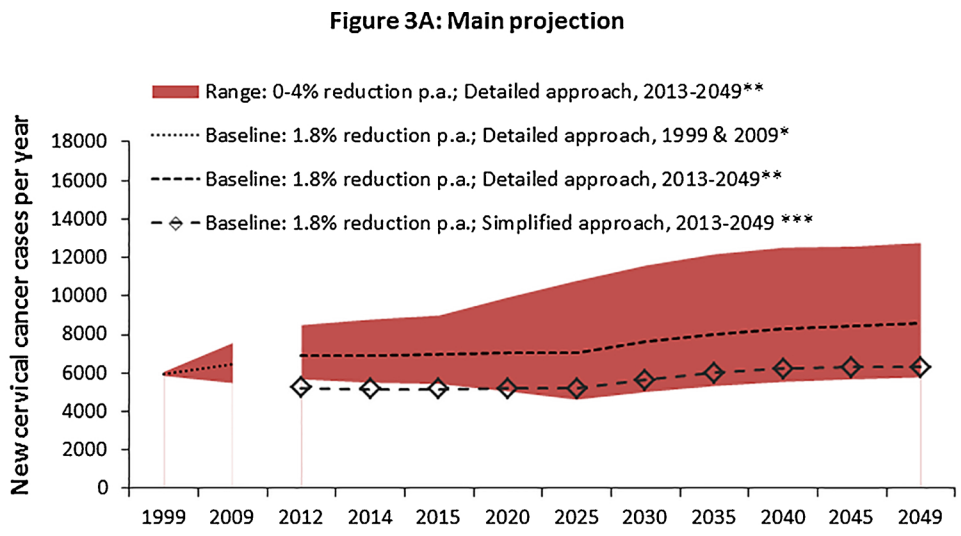
4. Discussion

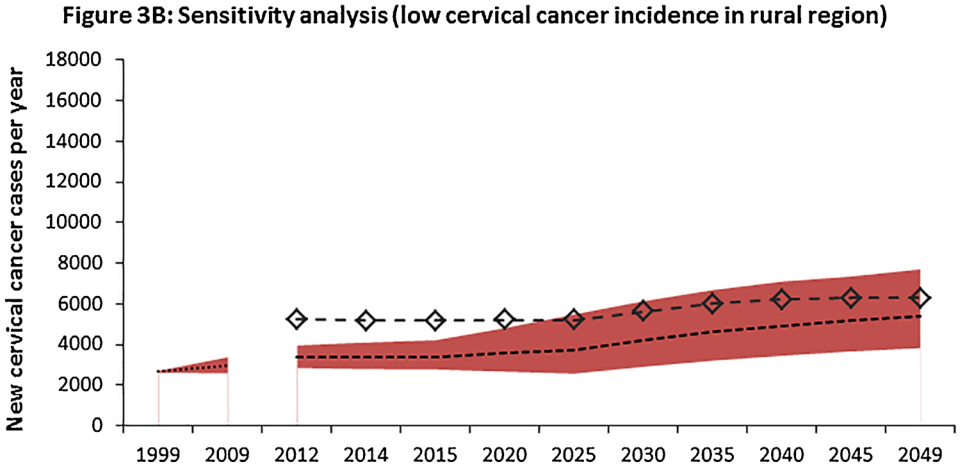
To our knowledge this is the first extensively detailed review of the burden of cervical cancer in Vietnam. The review has synthesised all presently available published sources in English and Vietnamese on the burden of HPV infection, HSIL precursor lesions, and cervical cancer incidence and mortality, as well as the available information on the correlates of HPV infection and cofactors for progression to cervical cancer in Vietnam. Additionally, our projection of the estimated number of new cervical cancer cases over the next 35 years provides important context for future assessment of the health and economic benefits of introducing widespread cervical cancer prevention approaches in Vietnam.

Using the available survey data, we estimated high-risk HPV infection prevalence in the general female population in Vietnam as 6%, although significant variation between regions, particularly north and south, was identified. Although all five cross-sectional HPV prevalence surveys were conducted in female populations with similar characteristics (the majority being married females, aged 15–69 years old), there were a number of factors that could lead to this variation, including differences in sexual behaviour, different time periods, and different HPV test technologies used among the surveys. It is also important to note that all the original studies were conducted in urban areas, while the majority of the Vietnamese population lives in rural areas, so these data may not be representative of the HPV prevalence in Vietnam in general. It will be important for future HPV prevalence surveys to focus on collecting data in rural areas. Based on the results of four cytological cervical screening projects for previously unscreened female populations in Vietnam, we found that the prevalence of HSIL in cytologically-screened women aged 35–60 years ranged from 0.4% to 1.3% in four large screening projects conducted from 1999 to 2010. However, given that HSIL prevalence was reported based on community-based screening projects, many issues regarding sampling strategy, subjectivity of cytologic interpretation, and/or data quality control may have impacted these results and may explain the relatively wide variation in the findings.

The evidence available suggests that Vietnamese women have a low exposure to the known HPV co-factors, with low, constant prevalence of oral contraceptive usage, a low and declining smoking prevalence, and a declining fertility rate [55,56,57,58,71,72]. However, there is some evidence of a trend towards an earlier age of sexual initiation and a higher occurrence of pre-marital sex, which is probably related to changes in socio-economic status in Vietnam over the last two decades (1990s–2000s) [53,73]. These changes (in the absence of any further intervention) may result in an increase in the incidence of cervical cancer in the next 30 years in Vietnam, potentially countered to some degrees by socio-economic development [32].

There are several limitations to the current study. While we did apply a systematic search strategy to our review, and considered Vietnamese-language publications, it is still possible that we have not captured all local data sources. Furthermore, in relation to our projections, the variable quality of the available data leads to considerable uncertainty in estimates of the burden of cervical cancer in the future. The cancer incidence rate for unscreened populations in other settings, which we used to inform projections for rural regions in the detailed approach was approximately 50% higher than the GLOBOCAN 2012 estimate for incidence in Vietnam as a whole, and given that the rural population currently comprises approximately 70% of the total Vietnamese population, these factors resulted in a substantially higher predicted number of new cervical cancer cases in the next 35 years in the detailed method compared to the simplified method based only on





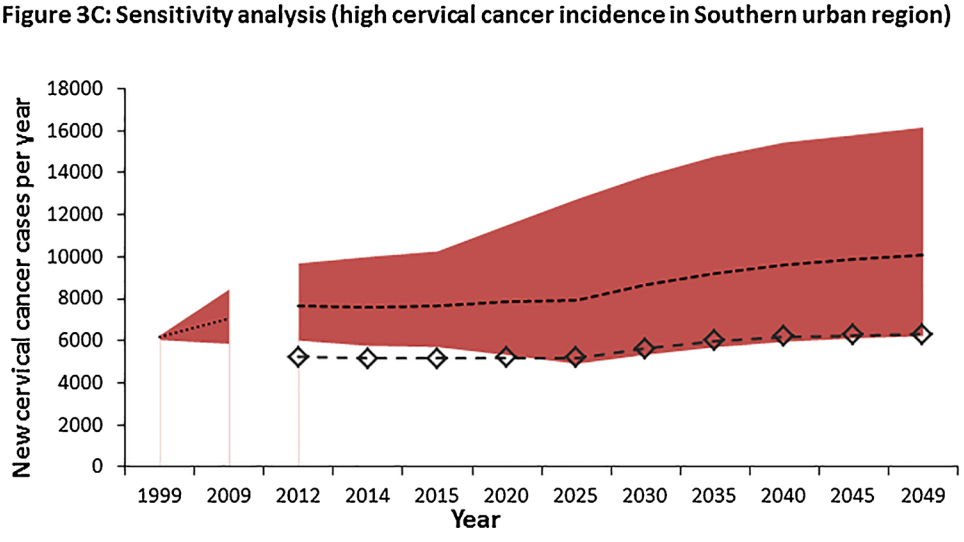


Fig. 3. Predicted number of new cervical cancer cases in Vietnam by year.
(*) Detailed approach, 1999, 2009: Using age-specific incidence obtained from the Hanoi cancer registry reported by IARC's CI5-VIII for the northern urban region, age-specific incidence from HCM city cancer registry reported by IARC's CI5-VIII for the southern urban region and average age-specific incidence for unscreened populations in less developed countries as reported by IARC's CI5-IX for rural regions; Using regional estimated-population data from Vietnam 1999 and 2009 population censuses. (**)Detailed approach, 2013-2049: Using age-specific incidence obtained from the Hanoi cancer registry reported by IARC's CI5-VIII for the northern urban region, age-specific incidence from HCM city cancer registry reported by IARC's CI5VIII for the southern urban region and average age-specific incidence for unscreened populations in less developed countries as reported by IARC's CI5-IX for rural regions; Using regional projected-population data based on Vietnam 2009 population census survey and 2014 intercensal population survey (using medium fertility rate). (***)Simplified approach: Using estimated GLOBOCAN 2012 age-specific cervical cancer incidence for Vietnam and using projected-population data based on Vietnam 2009 population census survey and 2014 intercensal population survey (using medium fertility rate). A reduction of 1.8% in cancer incidence each year was applied from 2009-2030 in both projection approaches. Ranges informed by sensitivity analysis taking into account alternate assumptions about ongoing trends in rates. See text of methods for detailed explanation.

GLOBOCAN 2012 estimated rates. We also had to assume, in the absence of other information, that similar rates of cervical cancer applied across rural regions of Vietnam, which may not be the case. Additionally, we could not directly take into account the effect of any changes in HPV infection correlates and cervical cancer cofactors, or the effect of opportunistic screening, over time. However, our review of data on the cofactors of progression to cervical cancer showed that current exposure to these factors is low and thus their impact on changes on future rates in the next few decades is likely to be limited. We did identify major changes in sexual behaviour in Vietnam over the

last few decades which may influence future cervical cancer rates. This would be counteracted to some extent by opportunistic screening initiatives and in our base case analysis we assumed that the net effect of these influences, in the absence of organised national interventions, would be a gradual reduction in cervical cancer rates over time in line with that observed in other middle-income countries. To take account of the uncertainties in all these influences we included a wide range of assumptions in our sensitivity analysis for the ongoing trends in cervical cancer rates. Results of our sensitivity analyses provided a wider range of new cervical cancer cases over the next 35 years in Vietnam. Finally, we did not take into account the impact of the rate of hysterectomies in the population in this projection. Although we are aware that hysterectomy would not be uncommon in Vietnam, to our knowledge these data are not available.

We identified several key points related to the burden of cervical cancer in Vietnam in this review. Firstly, the data for cervical cancer incidence and mortality in Vietnam are relatively limited. Our review found that although there are currently 6 cancer registries operating in provinces/cities in Vietnam, only the cancer incidence data from the Hanoi and HCMC cancer registries were reported by IARC for the period 1991–1993 (Hanoi), 1993–1997 (Hanoi), 1995–1998 (HCMC), and 2009–2012 (HCMC). Unfortunately, at the present time reliable data on cervical cancer mortality in Vietnam is not available, so that currently the most reliable estimates of cancer mortality are to be found in GLOBOCAN 2012.

Secondly, in both IARC-reported data (1990s and 2009–2012) and non-IARC reported data (2001–2008) a marked variation in cancer incidence was seen between northern cities/provinces (Hanoi, Hai Phong, Thai Nguyen) and southern cities/provinces (HCMC and Can Tho). Although there is a substantial reduction in the cervical cancer incidence in Ho Chi Minh City over the period 1995–2012, the most current cervical cancer rate (2009–2012) in HCMC still remain higher than the non-IARC-reported cancer rates of Hanoi and other northern provinces (2001–2008) (Appendix C, Table C1). This noticeable reduction of cervical cancer incidence in HCMC in the absence of both national cervical screening and HPV vaccination program could suggest that the peak of cervical cancer incidence rates reported for the period 1995–1998 in HCMC could be potentially associated with HPV exposure or exposure to the cofactors of HPV infection of that cohort in the past. Our review found that the differences in sexual behaviours between the north and south in older marriage cohorts (1960s–1970s) may explain the variation in cervical cancer incidence observed 20–30 years later (1990s). It is also possible that social conditions during and after the Vietnam War in the 1960s–1970s may have differentially affected the patterns of sexual behaviour of the populations in these regions [74,75]. In the north, family planning services have been in place since 1963, and have mainly provided contraceptive services [76]. Additionally, during the Vietnam War many men were away from home, and as social norms required women to be strictly monogamous it is assumed that sexual activities were limited for many women in the north during that period. In contrast, the war mainly happened in the south where millions of local and foreigner soldiers were stationed, and thus sex services flourished in this area [77]. Therefore, it is possible that more women were then exposed to high-risk sexual behaviours, including having multiple sex partners, having sexually transmitted diseases, and having more children, given that a family planning program had not been implemented at that time in the south. As a result, cervical cancer incidence was often recorded at high rates in southern provinces [78]. Alman et al. reviewed fertility rates in Vietnam and found that in 1969–1974 the fertility rate in the south was 6.6 per women, compared to 5.7 children per women in the north [55]. After the reunification in 1975 the government expanded family planning services throughout the whole country [76]. However, the fertility rate still remained slightly higher in the south than in the north (5.1 vs. 4.7) in 1974–1979 [55]. The differences in sexual behaviours and reproductive health care systems between the north and south of Vietnam during and after the war may help explain the variation of cervical cancer in two regions in the 1990s.

Thirdly, it is also important to note that both of the IARC reported cancer registries (1993-1998) were located in the two biggest cities of Vietnam, where the GDP per capita is and has been higher than the national average. Therefore, given that less than a third of the Vietnamese population live in urban areas over the same period, the data from these registries may not be representative of the cervical cancer incidence of the whole country. This demonstrates the importance of improving the quality of all local cancer registries to the level of IARC certification, particularly cancer registries operating in rural areas, so that available high quality data can provide a broader representation of cancer in the whole country.

Fourthly, based on the data for cervical cancer incidence summarised in our review, some questions about the data not only for local cancer registries but also of the IARC-reported registries of Hanoi and HCM city should be considered. The low cervical cancer incidence rates (ASR: 3.5–5.5/100,000) reported by the non-certified local cancer registries suggests the possibility of under-registration. These incidence rates are lower than the reported incidence from a number of developed countries with well-established national cervical screening programs, such as the UK (ASR: 6.8/100.000) and New South Wales, Australia (ASR: 5.3/100.000) for 2003–2007 [79]. Additionally, the Hanoi cancer registries have not been continuously reported by IARC since they were first certified in the 1990s and most recently the HCMC registry was reported on for the second time using data for 2009–2012. Issues relating to lack of continuous certification/inclusion in IARC reporting could be related to meeting the criteria for data completeness and validity [80]. It was noted in the methodology section of IARC's CI5, Volume VIII that only 75% and 85% of newly diagnosed cancer cases were histologically verified in these registries, and death certificates have not been used as a source of data [81]. Therefore, some under-registration or misclassification of cancer cases may have occurred in both the IARC-certified and non-IARC-certified cancer registries. The under-reporting of cancer incidence in the registries would probably result in underestimation of cancer incidence and mortality by GLOBOCAN 2012, which used data from non-IARC reported cancer registries – Hanoi (2007–2009) and HCMC (2006–2010) [70]. This underestimation issue might be similar to that identified in relation to the burden of cervical cancer in China as reported by Shi et al., 2012 [82].

The final issue identified by our review is that the central reason for the limited availability of official cervical cancer mortality data noted by IARC for the most recent reported HCMC cancer registry (2009–2012), is that death certificates have not been used to identify the cause of death in Vietnam. Rao et al., 2010, found that the mortality registration system in Vietnam has not complied with international standards for recording and reporting death cases by age, sex and cause [83]. According to the international recommendations for statistical classification of diseases and health related problems, the cause of death should be verified by a trained medical doctor and the diseases need to be coded in ICD-10 [84]. In Vietnam, for deaths that occurred outside health facilities, the cause of death is not ascertained by medical certification. Consequently, this could result in the misclassification of cause of death.

The issues this review identified in Vietnam regarding limitations in the availability of cancer data, the quality of cancer registry data, the lack of death certification in cause-of-death ascertainment, and the

variation in the burden of disease among regions are likely to be similar in many other LMICs. Curado et al. (2009), by reviewing population-based cancer registry data that reported to IARC, CI5-IX for the period 1998–2002, found that there were only a limited number of cancer registries from Africa and Asia included, which covered only 1% and 4% of the total population in each continent, respectively [85]. In Africa, among a total of 16 submitted cancer registries, only 5 cancer registries were included in CIV-IX. In Asia, only 44 cancer registries were reported among a total of 77 submitted cancer registries [85]. The issue of low-quality-cancer-registry data does not necessarily involve the registries per se, but it might be caused by gaps in the existing civil and health information registration system in LMICs [85]. Examples of these gaps could be not using a medical certificate to verify a cause of death, or lack of collaboration between different reporting sources. Only when these gaps are filled will cancer registry data from LMICs meet the criteria of completeness, validity, comparability, and timeliness required to be continuously certified and reported by IARC [86]. As a result, the improvement of civil and health information registration systems and cancer registry data will make high quality cancer data more available for disease monitoring and surveillance, as well as provide detailed information for the planning stages of future interventions in these countries [87]. The WHO Director-General has called for action towards the elimination of cervical cancer as a public health problem [88]. The completeness of data from LMICs will be a critical issue in future for evaluating the burden of disease and monitoring of the effectiveness of cervical cancer control interventions.

Our projections indicate that in the absence of a comprehensive national prevention strategy, the number of new cervical cancer cases diagnosed in Vietnam is expected to increase by 20% (range 0–50%) from 2012 to 2050, indicating that the implementation of cervical cancer preventive strategies is crucial. The WHO guidelines for cervical cancer prevention (2014) and more recently the American Society of Clinical Oncology (ASCO) resource-stratified guidelines for cervical screening (2016) have proposed a range of possible cervical screening strategies which could be affordable and accessible for LMICs like Vietnam, including possibilities for testing women once or a few times in their lifetime with HPV DNA-based screening [89,90]. Over the longer term, the widespread implementation of HPV vaccination also holds potential to substantially reduce the burden of cervical cancer in Vietnamese women. Our future work will use the findings of the current study to evaluate the most effective and cost-effective options for cervical cancer screening combined with HPV vaccination in Vietnam, as we have previously done for China and other countries [91].

5. Conclusions

Our study provides the most comprehensive review to date of the evidence on cervical cancer burden in Vietnam. The findings support efforts to identify strategies for effective funding and delivery of HPV vaccination and cervical screening in Vietnam, which could avert a substantial proportion of the several hundred thousand cervical cancer cases expected before 2050.

Author contribution

D. Nguyen: performed literature search, data extraction, and data analysis; drafted the manuscript; incorporated comments for the final version of manuscript.

K. Simms: substantial contribution in conceptualizing, guiding for cancer projection, supervising the whole process, and reviewing the manuscript.

H.Q.V. Nguyen, T.V. Tran, N.H. Nguyen: contributed in conceptualization, provided local data, provided local expert opinions, and reviewed the manuscript.

S. Lamontagne: formed conceptualisation and design of the study, advised on projection methods of new cancer cases, reviewed the manuscript.

P. Castle: contributed in conceptualization and design of the study, gave advice for the interpretation of results, reviewed the manuscript

K. Canfell: oversaw conceptualisation and design of the study, provided advice for data analysis and interpretation of results, reviewed the manuscript.

All authors approved the final manuscript.

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Conflicts of interest

None.

KC is co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia (‘Compass’) (NCT02328872), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. KC is also a PI on Compass in New Zealand, (‘Compass NZ’) (ACTRN12614000714684) which is conducted and funded by Diagnostic Medlab (DML), now Auckland District Health Board. DML received an equipment and a funding contribution for the Compass trial from Roche Molecular Systems. However, neither KC nor her institution on her behalf (Cancer Council NSW) receive direct or indirect funding from industry for these trials or any other project.

PC has received commercial HPV tests for research at a reduced or no cost from Roche, BD, Cepheid, and Arbor Vita Corporation.

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Appendix A. Systematic review on the prevalence of HPV and HSIL in Vietnam

Research question 1a: What is the prevalence of HPV infection among general Vietnamese female population?
Research question 1b: What is the prevalence of HSIL among general Vietnamese female population?

	Population	Outcomes
1a	Sexual active Vietnamese female population without symptoms of cervical pre-cancer or cancer	HPV prevalence
1b	Sexual active Vietnamese female population without symptoms of cervical pre-cancer or cancer	HSIL prevalence

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Table A1
Inclusion and exclusion criteria for question 1a and 1b.

Selection criteria	Inclusion	Exclusion
Study type	Prevalence/ rate	
Study design	Cross-sectional study/survey	
Study population	Asymptomatic Vietnamese women Random sample of general female population of Vietnam or province of Vietnam	Vietnamese women with symptoms or diagnosis with HPV infection or cervical pre-cancer or cancer. Populations drawn from clinics or health facilities High risk populations, eg HIV positive, sex workers, drug users.
Outcomes	Prevalence of cervical HPV infection (any HPV, hr-HPV) Prevalence of HSIL	Do not report on HPV prevalence of cervical HPV infection Do not report on HSIL prevalence
Language	English, Vietnamese	
Publication period	After 31st December 1989 to before 30 April 2017	

Table A2
Complete list of search terms used for the HPV and HSIL prevalence in general female population in Vietnam.

#	Searches	Results	Annotations
1	HPV.mp.	91746	
2	HPV.pt.	0	
3	hpv.mp.	91746	
4	hr$HPV.mp.	1499	
5	papillomavirus.mp.	99182	
6	human papillomavirus.mp.	84201	
7	Papillomavirus Infections/	22741	
8	HPV infection.mp.	24665	
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	119570	
10	HSIL.mp.	5201	
11	exp Cervical Intraepithelial Neoplasia/ or exp Uterine Cervical Neoplasms/ or exp "Squamous Intraepithelial Lesions of the Cervix"/	178113	
12	CIN*.mp.	313389	
13	exp Uterine Cervical Dysplasia/ or exp Cervix Uteri/ or exp Carcinoma, Squamous Cell/	329299	
14	cervix uteri.mp.	36473	
15	cervical intraepithelial neoplasia.mp.	23717	
16	uterine cervical neoplasm*.mp.	72361	
17	10 or 11 or 12 or 13 or 14 or 15 or 16	766420	
18	prevalence.mp.	1640721	
19	exp Prevalence/	899490	
20	exp Incidence/	652963	
21	incidence.mp.	1950205	
22	rate.mp.	5112231	
23	frequency.mp.	1870789	
24	proportion.mp.	841329	
25	18 or 19 or 20 or 21 or 22 or 23 or 24	9757201	
26	Vietnam.mp.	36840	
27	Hanoi.mp.	2924	
28	Ho Chi Minh.mp.	1843	
29	Ho Chi Minh city.mp.	1750	
30	Northern Vietnam.mp.	1312	
31	Southern Vietnam.mp.	955	
32	26 or 27 or 28 or 29 or 30 or 31	37705	
33	9 and 25 and 32	102	
34	limit 33 to english language	99	
35	limit 34 to human [Limit not valid in Global Health; records were retained]	97	
36	limit 35 to yr = "1986 -Current"	97	
37	remove duplicates from 36	53	
38	17 and 25 and 32	148	
39	limit 38 to english language	137	
40	limit 39 to human [Limit not valid in Global Health; records were retained]	127	
41	limit 40 to yr = "1986 -Current"	127	
42	remove duplicates from 41	88	
43	37 or 42	115	

Database(s): Embase Classic + Embase 1947 to 2016 December 01, Global Health 1910 to 2016 Week 46, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, Ovid MEDLINE(R) Daily Update November 29, 2016 Search Strategy.

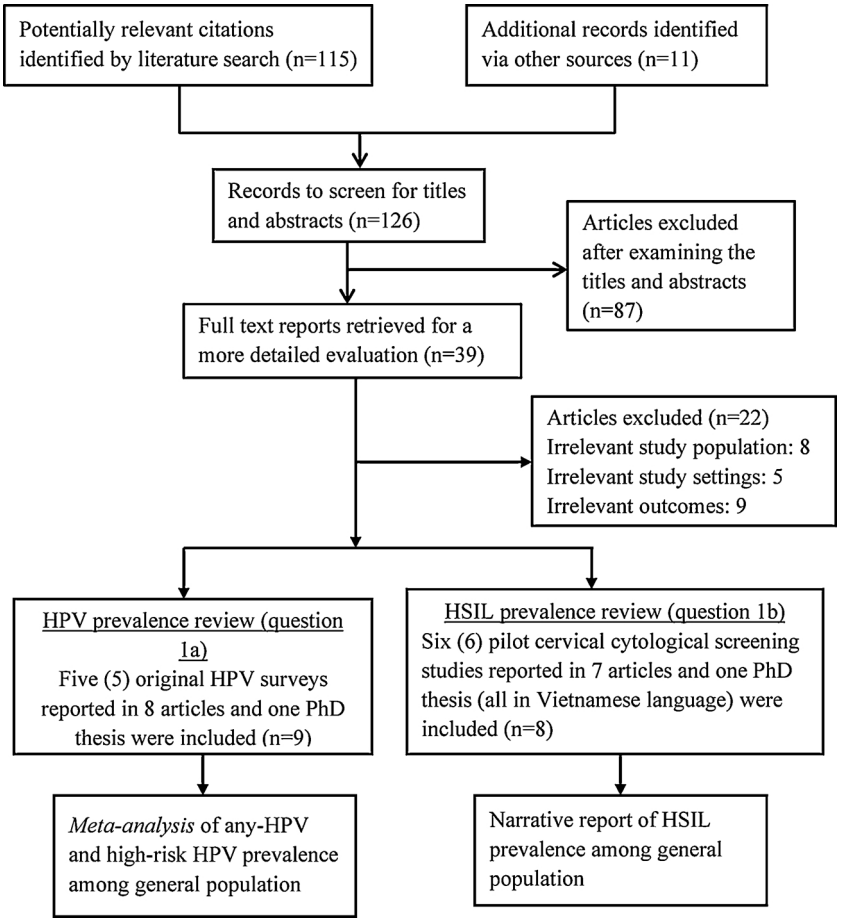

Fig. A1. Flow diagram of study selection process for the review of the prevalence of HPV infection and high squamous intraepithelial lesion among general population Viet Nam.

Appendix B. Systematic review of the factors correlated to the transmission of HPV and cofactors related to the progression to cervical cancer in Vietnam

Research question 2a and 2b: What risk factors can promote the transmission of HPV and the progression to cervical cancer among Vietnamese female population? Suggested risk factors include:

	Population	Outcomes
2a	Correlates to HPV infection	number of lifetime sex partners, age at sexual debut, STI exposure
2b	Cofactors of cervical cancer	oral contraception, smoking, parity and early age at first full term pregnancy

PICO Question 2a: In the Vietnamese female population are number of lifetime sex partners or age at sexual debut risk factors for cervical HPV infection?

PICO Question 2b: In the Vietnamese female population are oral contraceptive use or smoking or parity or early age at first full term pregnancy risk factors for cervical cancer?

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Table B1
PICO questions.

	Population	Exposure	Comparator/Reference group	Outcomes
2a	Sexual Vietnamese female population without symptoms or previous diagnosis of cervical cancer/pre-cancer	Any comparisons of different number of lifetime sexual partners		HPV infection
		Age of sexual debut < 16 years	Age of sexual debut ≥ 16 years	HPV infection
2b	Sexual active Vietnamese female population without symptoms or previous diagnosis of cervical cancer/pre-cancer	Ever used oral contraception	Never used oral contraceptives	Cervical cancer
		Current smoking	Never smoked or non-current smoker	
		Null-parity or Multiple parity	Having 1 to 2 children	
		Any comparisons of different ages at first full term pregnancy		

Table B2
Inclusion and exclusion criteria for 2a.

Selection criteria	Inclusion	Exclusion
Study type	Aetiology/Risk factor	
Study design	Cohort studies or nest case-control studies or systematic reviews of above. If no cohort studies achieved, broadened inclusion criteria: population based, cross-sectional studies, hospital-based case control	
Study population	Sexual active Vietnamese female population without symptoms of cervical cancer/pre-cancer	Vietnamese female population with symptoms of cervical cancer/pre-cancer or high risk populations (HIV positive, sex workers)
Exposure	Independently specify the exposure to number of lifetime sex partner	Do not specify the exposure to number of lifetime sex partner
	Independently specify the exposure of early age at sexual debut	Do not specify the exposure to early age at sexual debut
Comparator/Reference group	Do not clearly study the association between each factor with HPV infection	
Outcomes	Independently confirmed the association between number of lifetime sex partners and cervical HPV infection	Do not report on the association between number of lifetime sex partners and cervical HPV infection prevalence
	Independently confirmed the association between early age at sexual debut and cervical HPV infection	Do not report on the association between early age at sexual debut and cervical HPV infection prevalence
Language	English and Vietnamese	
Publication period	After 31st December 1989 to before 30 April 2016	

Table B3
Inclusion and exclusion criteria for 2b.

Selection criteria	Inclusion	Exclusion
Study type	Aetiology/Risk factor	
Study design	Cohort studies or nest case-control studies or systematic reviews of above	
Study population	Sexual Vietnamese female population without symptoms or previous diagnosis of cervical cancer/pre-cancer	Vietnamese female population with symptoms or previous diagnosis of cervical cancer/pre-cancer High risk populations, eg. HIV positive, sex workers
Exposure	Independently specify the exposure to oral contraception	Do not specify the exposure to oral contraception, smoking, parity or early age at first full term pregnancy
	Independently specify the exposure to smoking	Do not specify the exposure to smoking
	Independently specify the exposure to parity	Do not specify the exposure to parity
	Independently specify the exposure to early age at first full term pregnancy	Do not specify the exposure to early age at first full term pregnancy
Comparator/Reference group	Do not clearly study the association between each factor with cervical cancer	
Outcomes	Independently confirmed the association between oral contraception, smoking, parity and early age at first full term pregnancy and cervical cancer/pre-cancer	Do not report on the association between oral contraception, smoking, parity and early age at first full term pregnancy and cervical cancer/pre-cancer
Language	English and Vietnamese	
Publication period	After 31st December 1989 to before 30 April 2017	

Table B4
Search terms for correlates and cofactors of HPV infection and cervical cancer in Vietnam.

#	Searches	Results	Annotations
1	HPV.mp.	91655	
2	hpv.mp.	91655	
3	hr$HPV.mp.	1499	
4	papillomavirus.mp.	99070	
5	human papillomavirus.mp.	84201	
6	Papillomavirus Infections/	22741	
7	HPV infection.mp.	24665	
8	1 or 2 or 3 or 4 or 5 or 6 or 7	119367	
9	HSIL.mp.	5201	
10	exp Cervical Intraepithelial Neoplasia/ or exp Uterine Cervical Neoplasms/ or exp "Squamous Intraepithelial Lesions of the Cervix"/	172611	
11	CIN*.mp.	304093	
12	exp Uterine Cervical Dysplasia/ or exp Cervix Uteri/ or exp Carcinoma, Squamous Cell/	318583	
13	cervix uteri.mp.	34644	
14	cervical intraepithelial neoplasia.mp.	23705	
15	uterine cervical neoplasm*.mp.	72361	
16	cervical cancer.mp. or exp cervical cancer/	183981	
17	cervical precancer.mp.	686	
18	((cervi* or uteri*) adj3 (cancer or carcinoma)).mp.	186475	
19	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	785235	
20	exp Vietnam/ep [Epidemiology]	2655	
21	Vietnam.mp.	36289	
22	Hanoi.mp.	2880	
23	Ho Chi Minh.mp.	1839	
24	Ho Chi Minh city.mp.	1747	
25	Northern Vietnam.mp.	1308	
26	Southern Vietnam.mp.	952	
27	20 or 21 or 22 or 23 or 24 or 25 or 26	37208	
28	exp Sexual Behavior/ or sexual behaviour.mp.	306572	
29	exp Sexual Partners/ or sex partner.mp.	257649	
30	(number adj4 partner*).mp.	12374	
31	exp Sexually Transmitted Diseases/ or sexual transmitted disease.mp.	471694	
32	STD.mp. or Sexually Transmitted Diseases/	84606	
33	(age at first sex* adj3 (intercourse or debut)).mp.	707	
34	28 or 29 or 30 or 31 or 32 or 33	771517	
35	oral contraceptive.mp. or exp Contraceptives, Oral/	117052	
36	exp Contraceptives, Oral, Hormonal/ or exp Contraceptives, Oral, Combined/ or contraceptive pill.mp. or exp Contraception/	233872	
37	family planning.mp. or exp Family Planning Services/	94636	
38	((side or adverse or undesirable) adj2 (effect* or reaction* or event* or outcome*) adj2 oral contracept*).mp.	3904	
39	35 or 36 or 37 or 38	327360	
40	((side or adverse or undesirable) adj2 (effect* or reaction* or event* or outcome*) adj2 smok*).mp.	1657	
41	smok*.mp.	784036	
42	exp Smoking/	441975	
43	40 or 41 or 42	784036	
44	parity.mp. or exp Parity/	94229	
45	(number adj2 born child*).mp.	23	
46	44 or 45	94243	
47	age of first full term pregnancy.mp.	412	
48	(age adj4 pregnanc*).mp.	19623	
49	47 or 48	19927	
50	8 and 27 and 34	55	
51	19 and 27 and 39	4	
52	19 and 27 and 43	24	
53	19 and 27 and 46	10	
54	19 and 27 and 49	0	
55	remove duplicates from 50	35	
56	remove duplicates from 51	3	
57	remove duplicates from 52	15	
58	remove duplicates from 53	4	

Database(s): Embase 1974 to 2016 November 30, Global Health 1910 to 2016 Week 46, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present Search Strategy.

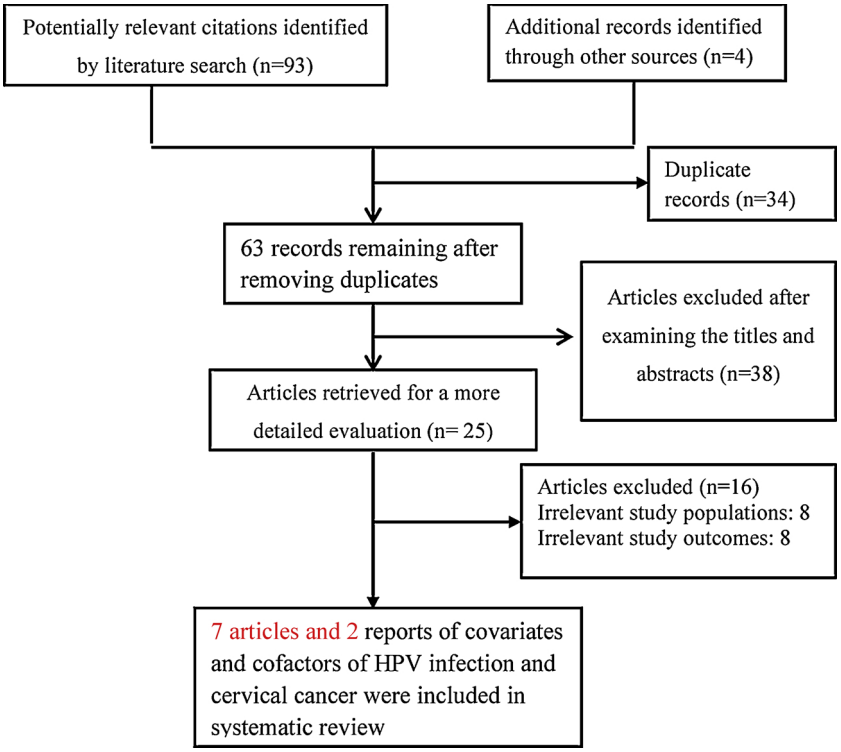

Fig. B1. Flow diagram of study selection for the review of covariates and cofactor of HPV infection and cervical cancer.

Appendix C. Currently available sources of cervical cancer incidences in Vietnam

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Table C1
Cervical cancer incidence reported from local cancer registries to Viet Nam NCI.

Data source	GDP per capita ratio (2001-2013	2001-2004 NCI report 2001-2004	2004-2008 NCI report 2004-2008
Number of cancer registries		*5*	*6*
Number of registries with cervical cancer ranked in the 10 most common cancer		*5/5*	*6/6*
Cervical cancer incidence (ASRW) per 100.000 women			
Thai Nguyen	0.31	3.8 (Northern, Rural, mountainous)	3.5 (Northern, Rural, mountainous)
Hai Phong	1	4.0 (Northern, Coast)	5.5 (Northern, Coast)
Ha Noi	1.53-1.75	9.5 (Northern, Urban)	10.5 (Northern, Urban)
Hue	0.55	5.0 (Central, Rural)	4.7 (Central, Rural)
Can Tho	1.6-2.1	20.8 (Southern, Urban)	19.6 (Southern, Urban)
Ho Chi Minh city	2.09-2.46		15.3 (Southern, Urban)

Table C2
GDP per capita in cancer registry sites in Vietnam.
Source: Vietnam Government Statistics Office and Provincial Statistic Offices.

	2001	2009	2010	2011	2012	2013	Ratio of provincial/city GDP and national average GDP
National average GDP	449	1,089	1,139	1,396	1,746	1,886	***1***
Hanoi	787	1,834	1,858	2,277	2,671	2,979	***1.53 - 1.75***
Hai Phong							***1***
Thai Nguyen		823					***0.31***
Hue		1,003	1,151	1,300	1,490		***0.55***
HCM city	1069	2,652	2,799	3,203	3,647	4,515	***2.09 - 2.46***
Can Tho			2,350			3,013	***1.6 - 2.1***

Unit: USD.

Appendix D. Projection methods

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Table D1
Summary of projection methods of cervical cancer new cases in Vietnam for the year 1999, 2009 and 2013-2049.

Data	Brief data description	Data sources
1. Detailed projection (regional-specific assumptions)		
1.1 Estimated cervical cancer cases for 1999 and 2009		
Population data	Northern urban (~15% of total population); Southern urban (~15% of total population); Rural (~70% of total population)	1999 and 2009 population census [27,28]
Age-specific cervical cancer incidence	Ha Noi cancer registry for Northern urban;	IARC's CIV, volume VIII [22] (Hanoi)
	Ho Chi Minh cancer registry for Southern urban	IARC's CIV, volume XI [23] (HoChiMinh City)
	Unscreened population of developing countries for rural region	IARC's CIV, volume IX (less developed countries [29]
	The cervical cancer incidence rates were adjusted for trends over time	Bray et al, 2012 [32]
1.2 Projected new cervical cancer cases for 2013-2049		
Population data	Northern urban (~15% of total population);	2009 population census (using medium fertility rate level) [31]
	Southern urban (~15% of total population); Rural (~70% of total population)	2014 intercensal population census (using medium fertility level)[30]
Age-specific cervical cancer incidence	Ha Noi cancer registry for Northern urban;	IARC's CIV, volume VIII [22] (Hanoi)
	Ho Chi Minh cancer registry for Southern urban	IARC's CIV, volume XI [23] (HoChiMinh City)
	Unscreened population of less developed countries for rural region	IARC's CIV, volume IX (less developed countries [29]
2. Simplified projection for 2013-2049 (assumptions for the country as a whole or simplified approach)		
Population data	Projected population for 2013-2049 for Vietnam as a whole	2009 population census (using medium fertility rate level) [31] 2014 intercensal population census (using medium fertility level)[30]
Age-specific cervical cancer incidence	Estimated cervical cancer incidence for the country as a whole	GLOBOCAN 2012 [1]
	The cervical cancer incidence rates were adjusted for trends over time	Bray et al., 2012 [32]

Appendix E. Additional findings of the review of the prevalence of HPV infection in Vietnam

See Fig. E1, .
Tables E1 and E2.

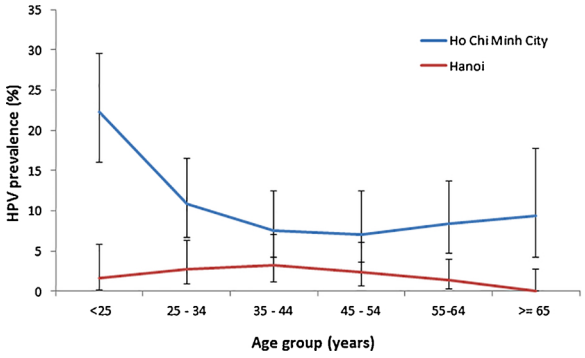

Fig. E1. Age-specific prevalence of HPV infection in normal cytological women in Hanoi and Ho Chi Minh City, IARC survey 1997 [92].

Table E1
Summary of population-based HPV prevalence studies in Vietnam.

No	Author	Published year	Study period	Setting	Study design	Study subjects	Sample size	HPV testing technique
1	Anh Pham [35]	2003	1997	Hanoi	Population-based	Married women aged 15-65 yrs	994	HPV GP5+/6+ primer-mediated PCR
			1997	Ho Chi minh City	Population-based	Married women aged 15-65 yrs	922	Yes
2	Hanh La [37]	2006	2004	Hanoi	Population-based	Married women aged 15-65 yrs	1231	HPV MY09/11 primer-mediated PCR
3	Ly Tran [38]	2015	2008-2009	Ho Chi Minh City	Population-based	Married women aged 18-69 yrs	1550	HPV MY09/11 primer-mediated PCR
4	Lan Vu [39, 40]	2011, 2013	2010 - 2011	Hanoi	Population-based	Married women aged 15-69 yrs	750	Real time PCR genotype Reverse Dot Blot (RDB) kit
				Ho Chi minh City	Population-based	married women aged 15-69 yrs	750	
				Thai Nguyen	Population-based	married women aged 15-69 yrs	1000	
				Hue	Population-based	married women aged 15-69 yrs	1000	
				Can Tho	population-based	married women aged 15-69 yrs	1000	

Table E2
HPV prevalence in invasive cervical cancer and high-grade intraepithelial neoplasia in Vietnam and neighbouring countries.

Study population	Study design	Group (mean age)	Number of cases	Crude HPV positive % (95%CI)	HPV 16/ HPV 18	Single Infection rate, 95% CI	Multiple infection rate, 95% CI
Vietnam [93]	Hospital-based, cross-sectional	ICC (47.46)	134	97.0 (92.5-99.2)	50%/35.4%	91.5 (85.4-95.7)	6.2 (2.7-11.8)
		HSIL (43.13)	126	93.7 (87.9-97.2)	46.6%/5.8%	83.9 (76.0-90.0)	15.3 (9.3-23.0)
Malaysia [93]	Hospital-based, cross-sectional	ICC (52.86)	101	96 (90.2-98.9)	38.1%/ 26.8%	88.7 (80.6-94.2)	3.1 (0.6-8.8)
		HSIL (49.30)	73	95.9 (88.5-99.1)	37.1%/8.6%	71.4 (59.4-81.6)	18.6 (10.3-29.7)
The Philippine [93]	Hospital-based, cross-sectional	ICC	103	84.5 (76.0-90.9)		90.8 (82.7-95.7)	8 (3.3-15.9)
		HSIL	6	100 (54.0-100.0)		66.7(22.3-95.7)	0
Thailand [94]	Hospital-based, case-control	ICC	416		50.9%/ 23.1%	66.6%	24.3%
		HSIL	100		44.2%/4.8%	61%	33%
Asian region [95]	Retrospective cross-sectional	ICC	2,994	88.2 (87.0-89.3)	60%/11%	95%	5%
Global [96]	Meta-analysis	ICC	30,848	89.9 (88.2-91.3)	56.6%/16%	79.0%	11.2%

Data sources: Quek et al, 2013 [93]; Chichareon et al 1998 [94]; de Sanjose et al, 2010 [95] and Smith et al, 2007 [96].

Appendix F. HPV prevalence and cervical cancer incidence of main cities/provinces in Viet Nam and other Asian countries

Table F1.

Table F1
Comparison of HPV prevalence and cervical cancer incidence rates (per 100.000 women) of Ha Noi and Ho Chi Minh city and selected populations in Asia region.

Population	Age standardized HPV prevalence (%, 95% CI)[92]	Cervical cancer incidence (1993-1997)[22]	National GDP per capita in 1998 [97]
Lampang, Thailand	9.6 (7.5-11.7)	24.2	1837
Songkhla, Thailand	3.8 (2.1-5.5)	16.6	1837
Busan, Korea	14.8 (5.8-23.8)	21.1	8134
Tamil Nadu, India	16.8 (14.9-18.8)	65.4	425
Ha Noi, Vietnam	1.6 (0.8-2.4)	**6.7**	361*
Ho Chi Minh city, Vietnam	11.4 (9.1-13.6)	**28.8**	361**

CI: Confidence Interval; GDP: Gross Domestic Product; *Ha Noi's GDP per capita is 1.7 times higher than the national average; ** Ho Chi Minh city's GDP per capita is 2.4 times higher than the national average.

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