Current Perspective

Primary prevention of human papillomavirus-dependent neoplasia: No condom, no sex

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Abstract

Cervix cancer is one of several neoplastic disorders that arise following transfer of human papillomavirus (HPV) during unprotected sexual intercourse, and like most other sexually transmitted diseases (STDs), is largely preventable by consistent condom use. This primary prevention strategy has received little support, however, when compared with massive secondary prevention initiatives involving cervical screening. The reasons for this anomalous situation are complex, and include: (i) the asymptomatic nature of most primary HPV infections; (ii) widespread ignorance concerning the venereal aetiology of HPV-related cancers; (iii) the common but incorrect belief that condom use does not reduce HPV transmission; (iv) the perceived irrelevance of safe sex campaigns based on reducing transmission of human immunodeficiency virus (HIV) in high-HPV but low-HIV countries such as the Philippines; (v) the promotion of oral contraception by the medical and pharmaceutical sectors as the sexual prophylaxis of choice; and (vi) the assumption that HPV vaccines will solve the problem. Here it is proposed that the high prevalence of non-HIV STDs, including distressing disorders such as genital warts and herpes simplex, can be exploited with greater efficacy as a public health deterrent to unsafe sex and HPV transmission. Targeting a "mutually assured infection" campaign at vulnerable subgroups such as teenagers and oral contraceptive users could help reverse the global expansion of HPV-related cancers.
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1. Introduction

The neoplastic sequelae of viral sexually transmitted viral diseases (STDs[1]) include cervical, penile, vulvar, vaginal and anal cancers (HPV), leukaemias and lymphomas (HTLV1, HIV/EBV), Kaposi sarcomas (HIV/HHV8), and hepatocellular carcinoma (HBV). Each year these viruses give rise to half a million new malignancies, accounting for up to 50% of cancers in some undeveloped countries [1]. As serious as this morbidity seems, however, it is barely one-thousandth the prevalence of the subclinical STD epidemic that now afflicts 500 million people worldwide [2].

Why the epidemic? All STDs are transmitted by the world's favourite risk behaviour: unsafe sex, defined here as any sexual activity involving contact with body fluids ('safe sex' denotes consistent and correct barrier prophylaxis, where 'consistent' indicates both past and present use, 'correct' implies an additional five criteria [3,4], and 'barrier prophylaxis' comprises use of the male condom with or without a diaphragm, cervical cap, or female condom). Being an HPV-transmitted disease [5], cervix cancer is part of a spectrum of neoplastic

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[1] Abbreviations: STD, sexually transmitted disease; HPV, human papillomavirus; HBV, hepatitis B virus; HTLV, human T cell lymphotropic virus; HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; HHV8, human herpes-like virus 8; HSV, herpes simplex virus; CSW, commercial sex worker.

STDs that is preventable by condom usage [6,7]. The ongoing public health failure to exploit this opportunity is considered below.

2. The problem

Person-to-person transmission of infections by unprotected sex has been occurring for millennia [8], making the 20th-century invention of antimicrobial drugs a turning-point in sexual history. For women, however, prevention of pregnancy has long been an even more urgent prophylactic priority. By freeing females from fear of fertilization, the arrival of the oral contraceptive in 1961 unleashed a reproductive revolution: traditional preoccupations with cervical mucus, caps, condoms and *coitus interruptus* were suddenly vanquished, converting sex from a primarily procreational to recreational activity. One effect of the Pill's popularity has been that condom-based prophylaxis is now the usual practice of only about 25% of sexually active individuals worldwide [9]; of note, the latter figure applies not only to poor countries but also to developed-world settings involving educated cohorts [10] such as college students [11] and medical trainees [12]. At least 80% of unmarried females who use hormonal contraception omit using additional ("double-dutch") barrier prophylaxis, reflecting low perceived need of condoms in the presence of alternative contraception [13]. Consistent with this, hormonal contraceptive use is associated with microbial infections such as *Chlamydia* and *Mycoplasma* and other STD sequelae [14]. The increase in infection risk associated with hormonal contraception [15] is preventable by consistent condom use [16].

HPV is the largest single contributor to the global incidence of STD: 15% of sexually active American teenage girls are infected each year [17] by one or more of the anogenital varieties of this virus [18], and the prevalence of active HPV infection in young women varies by region in the range 20–70% [19,20]. Over 75% of Americans have been infected by HPV at some time, with six million new genital HPV infections per annum in the US accounting for 40% of all sexual infections [21]; case-control data suggest an increased risk in oral contraceptive users [22]. Since HPV is not transmitted by semen, condom usage has long been assumed to be less effective than for other STDs such as gonorrhoea or HIV [23]; yet in sharp contradiction to this negative assumption, numerous studies have now confirmed inverse relationships between condom usage and HPV transmission [24], persistence [25] and seropositivity [26].

HSV2 is the other major viral STD, chronically affecting about 25% of the sexually active US population, three-quarters of whom are unaware of their infected status [27]; HSV also renders infected individuals hypersusceptible to co-infection with HPV [28].

Acknowledged as an excellent index of past infection, and hence of unsafe sex, HSV2 seroreactivity averages 50–60% in attendees of STD clinics [29] and about 80% in commercial sex workers (CSWs) [30]. Hence, as with long term oral contraceptive use, the increased cervix cancer risk recognised in HPV-positive populations who have also been infected with HSV2 [31] could plausibly relate to other correlates of unsafe sex.

The expansion of the STD epidemic in the second half of the 20th century reflects a coalescence of risk behaviours. Habitual practitioners of unprotected sex are more likely to have casual sexual partners [32] and also to engage in drug abuse [33]; the opportunities for infection of multiple parties via multiple routes may thus be exponentially increased. By the same token, higher rates of unplanned pregnancy occur in the same cohorts as incur STDs, irrespective of alleged contraceptive practices [34]. Growth in occupational and leisure travel [35], ethnic mixing [36], and sexual consumerism [37] has likewise increased international sexual contacts to a level unanticipated half a century ago. Rising STD transmission is often attributed to CSWs, particularly in developing countries, but the reality in developed countries is different; where CSWs are educated to practice safe sex [38], professional sexual encounters are significantly less hazardous than casual liaisons or one-night stands [39]. Patterns of sexual behaviour and STD transmission differ between countries, socioeconomic strata, and ethnic groups [40], making it inappropriate to generalise about public health strategies.

Higher frequency of intercourse has been associated with both HPV infection [41] and cervix cancer [42] in case-control studies. If considering only HPV-positive cohorts, such 'dose–response' correlations are apparent between cervical neoplasia and intercourse frequency [43], as well as with co-infection by other STDs [44], bacterial vaginosis [45], or *Chlamydia* spp. [46]. Infection with multiple HPV subtypes of differing oncogenicity [47] is demonstrable in 10–30% of HPV-positive individuals [48,49] and correlates with outcome [50,51] – when the type and number of infecting HPVs are controlled, the risk of cervix cancer becomes less dependent upon the number of sexual partners [52]. Health behaviours may therefore be improved by stressing the multiplicative nature of the risks specific to unsafe sex, as distinct from those of sexual activity or promiscuity *per se*.

The benefits of safe sex likewise appear multiplicative – that is, a small percentage rise in population condom usage can be expected to yield a proportionately larger reduction in STD transmission [53]. Moreover, longer durations of safe sex in women infected by high-risk HPV correlate with lower risks of cervical neoplasia [54], while regression of established neoplasia is accelerated by resumption of safe sex compared to continuation of unprotected sex [55,56]. These findings support the 'dose-dependent' nature of the relationship between

cervix cancer and unsafe sex, while weakening the credibility of a one-hit infectious aetiology that could theoretically be promoted by safe sex. The precise mechanistic basis for the presumed multi-hit sequelae of unsafe sex remains to be clarified.

Cervical screening rates correlate with oral contraceptive use independent of socioeconomic status [57], suggesting that the risks of acquiring HPV-dependent neoplasia from habitual unprotected sex may be discounted in the public mind by such screening. In fact, long-term oral contraceptive users remain at 3- to 4-fold higher risk of developing invasive cervix cancer than nonusers, irrespective of screening for preinvasive disease [58]. The undoubted efficacy of screening programs [59] is thus no reason for complacency.

3. The solution

Latex condoms are impermeable to most viruses [60], consistent with observed safe sex-dependent reductions of HPV [61,62] (including genital warts [63] and cervix cancer [64]), HSV1/2 and HIV infections [65,66]. Despite such evidence of efficacy, however, condoms continue to receive a bad press. In particular, many studies implicating the number of sexual partners as the prime STD risk factor have failed to document a protective effect of 're-ported condom usage' [67]. Such results are widely interpreted as signifying the unreliability of condoms for HPV prevention [68], but the data themselves are confounded by higher risks of the sexually active population who use condoms [69]. Estimates of safe sex-dependent STD risk reduction as low as 83–87% [70] (i.e., a failure rate as high as 15%) are attributed by default to condom breakage and slippage. However, since the incidence of these latter events is less than 2% [71], the real reason for failure remains unaccounted. The most likely explanation for this discrepancy is misreported usage: either discounted episodes of unsafe sex due to dissatisfaction with the alternative [72] – typically occurring with 'trusted' partners, and confounding 7–43% of such reports [73] – or else restriction of condom usage to the pre-ejaculation period (i.e., as a contraceptive measure alone) which may confound a further 11% [74]. Hence, the main shortcoming of barrier prophylaxis does not appear to be mechanical failure, as popularly believed, but lack of consistent and correct usage [75].

Few health hazards are associated with safe sex – indeed, some studies have pointed to health benefits [76] – yet cultural and moral sensitivities remain a major impediment to its promotion. Concerns that advocacy of protected sex may inadvertently encourage the other "three Ps" (premarital sex, promiscuity, and prostitution) damage the political correctness of 'safe sex education' in many communities [77] even though evidence for a promiscuity-promoting effect of safe sex education is

lacking. In contrast, unsafe sex is clearly related to a scarcity of safe sex education [78]. Public health campaigns promoting safe sex have enhanced condom usage rates by about 25% in absolute terms [79], and have been accompanied by a decline in both STD seroprevalence and cervix cancer among well-educated cohorts [80]. Even in disadvantaged subgroups such as CSWs, safe sex rates can approach 100% [81], whereas simple endorsement of abstinence or monogamy has proven ineffective as a strategy for reducing STD transmission in many studies [82].

There is little meaningful comparison to be made between advocating safe sex as a good idea and successfully entrenching a new behavioural norm. Consistent with this, recent studies have suggested a lack of benefit for traditional sex education in reducing risk behaviours [83]. Even the fear of HIV infection has failed to bring about behavioural transformation: among couples of differing HIV status, only about 50% practice safe sex [84]. These findings emphasize that scaremongering alone may not reduce risk-taking, and could prove counterproductive for the prevention of high-prevalence but low-awareness chronic infections such as HPV [85]; the assumption that AIDS awareness programs are the best tactic for controlling the broader STD epidemic may thus not turn out to be correct. In addition, regular condom usage may not be a realistic expectation for stable or monogamous couples, many of whom may opt to accept the limited risks of unprotected sex within the security of a long term relationship.

A more effective way to promote safe sexual practices among non-stable couples may thus depend less on emphasizing the small absolute risk of dying from contact with a sexual partner who happens to be infected with HIV – a risk which many sexually active individuals may perceive to be small – and more on educating young people about the much higher prevalence of non-lethal but troublesome STDs such as genital warts and herpes. In support of this "mutually assured infection" deterrent strategy, underestimation of infective risk among potential partners has recently been confirmed to be a key predisposition to STD transmission [86]. If such knowledge can be imparted through high-impact photographic materials – as have been used to deter individuals from sun tanning [87] – more extensive behavioural change may be achievable. However, careful preliminary research is still needed to test this hypothesis, and to ensure that deterrence in the target group can indeed be promoted through such aversive strategies.

4. Conclusion

Microbes love human sex – not because it is unhealthy, but because physical intimacy creates the

shortest distance between an infected host and an uninfected recipient. In terms of human behaviour, unsafe sex with an HPV-infected (albeit asymptomatic) partner is a primary independent risk factor for cervix cancer – a state of affairs that will persist until safe sex becomes the norm for young sexually active people [88], with other contraceptive practices shifting to an adjuvant role. The sexual precaution of choice for young people should therefore be either condoms or 'double-Dutch' contraception [89].

With hundreds of millions of people already affected, the STD epidemic constitutes a major long term threat to human health and cancer control. The risks of unsafe sex are multiplicative, both for individuals and for populations, but the good news is that the benefits of effective safe sex education are similarly synergistic. Greater public awareness of high-prevalence genital infections could thus prove more effective in changing risk behaviours than the scare strategies of the past, particularly in societies with low HIV prevalence. The aim of any such public health campaign – which should target its most potent warning images to young males, who may often resist negotiation to use condoms – should be to create a new sociocultural norm of "No condom, no sex".

Conflict of interest statement

None declared.

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