Lifestyle and socio-demographic factors associated with high-risk HPV infection in UK women

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The world age-standardised prevalence of high-risk HPV (hrHPV) infection among 5038 UK women aged 20–59 years, with a low-grade smear during 1999–2002, assessed for eligibility for TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears) was 34.2%. High-risk HPV prevalence decreased with increasing age, from 61% at ages 20–24 years to 14–15% in those over 50 years. The age-standardised prevalence was 15.1, 30.7 and 52.7%, respectively, in women with a current normal, borderline nuclear abnormalities (BNA) and mild smear. In overall multivariate analyses, tertiary education, previous pregnancy and childbirth were associated with reduced hrHPV infection risk. Risk of infection was increased in non-white women, women not married/cohabiting, hormonal contraceptives users and current smokers. In stratified analyses, current smear status and age remained associated with hrHPV infection. Data of this type are relevant to the debate on human papillomavirus (HPV) testing in screening and development of HPV vaccination programmes.

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Infection with human papillomavirus (HPV) is necessary for the development of cervical cancer (Walboomers et al, 1999; Bosch et al, 2002). Around 40 HPV types infect mucosal surfaces of the lower genital area (International Agency for Research on Cancer, 2005) and are broadly classified into high- or low-risk for cervical cancer (Manoz et al, 2003). Testing for high-risk HPV (hrHPV) DNA has the potential to improve cervical screening (Brink et al, 2005). In addition, following encouraging trial results (Harper et al, 2004; Villa et al, 2005), two HPV vaccines are under licence. The effectiveness and cost-effectiveness of incorporating HPV testing into screening, and of vaccine programmes, will partly depend on current HPV prevalence, infection patterns and factors associated with infection within specific populations.

Human papillomavirus population prevalence mainly depends on patterns of sexual exchange (International Agency for Research on Cancer, 2005), which vary between and within countries, by, for example, birth cohort and ethnic group (Johnson et al, 2001; Fenton et al, 2005). Most available data on HPV prevalence and associated factors are from the United States of America, and/or focus on young women; many series are highly selective and may lack generalisability. Other series did not examine lifestyle risk factors (e.g. Cuzick et al, 2003; Cuschieri et al, 2004; Moss et al, 2004; Hibbitts et al, 2006; Kitchener et al, 2006). Most infections in women under 30 are transient (Koutsky and Kiviat, 1999; Nobbenhuis et al, 2001; Woodman et al, 2001); infection risk factors, and/or their relative importance, may differ between young and older women. In addition, while cytological smear grade is strongly associated with HPV prevalence (Cuzick et al, 2003; Cuschieri et al, 2004), it is less clear whether the relative contribution of lifestyle risk factors differs by smear grade. We investigated factors associated with prevalence of hrHPV types in a large series of UK women and compared them in younger and older women and by cytological smear grade.

MATERIALS AND METHODS

Study population

Subjects were women assessed for eligibility for TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears), a randomised controlled trial (RCT) of alternative management policies and HPV triage (TOMBOLA Group, 2006).

Women aged 20–59 years, resident in Grampian, Tayside or Nottingham, with a low-grade smear (mild dyskaryosis or borderline nuclear abnormalities (BNA)) taken routinely in the UK national cervical screening programmes (CSPs) during 01/10/
Epidemiology

risk HPV prevalence was age-standardised to the truncated (20–59 years) women were classified hrHPV negative (hrHPV +ve) implying they carried at least one of the hrHPV strains. Other factors significantly associated with hrHPV status in multivariate analyses, non-white women (e.g. black-African, Indian, Pakistani) were at significantly increased risk. Single, and divorced/separated/widowed, women had significantly higher infection risk than married/co-habiting women. High-risk HPV infection was associated with never being pregnant, having had children and age at first pregnancy, but not with number of children or caesarean delivery. Combining pregnancy, childbirth and age at first pregnancy (as ‘reproductive history’), having a pregnancy resulting in childbirth was associated with lower infection risk, particularly for a first pregnancy at age ≥20 years. Current and previous oral contraceptive (OC) use (combined or progesterone-only), and current use of other hormonal contraception (e.g. implants, injections, intrauterine system), were associated with increased risk. Compared with never smokers, current smokers (but not ex-smokers) were at a modest increased risk, unrelated to smoking pack-years (data not shown). Barrier contraception and physical activity were also unrelated to risk.

In multivariate age-stratified analyses of women aged 20–29 years, age and smear status were significantly associated with infection. Tertiary education and having had children were also significant risk factors, with risk estimates similar to those in unstratified analyses. In women aged 30–59 years, age and smear status were significantly associated with infection, as were tertiary education, having had children, ethnicity and smoking; effect sizes were similar to those in Table 1. Other significant factors were marital status (increased risk in divorced/separated/widowed
women (odds ratio (OR) 2.23, 95% CI 1.79–2.79) and single women (OR 1.84, 95% CI 1.35–2.50), current hormonal contraceptive use (OR user vs non-user 1.30, 95% CI 1.03–1.64) and physical activity (OR active vs not active 0.76, 95% CI 0.60–0.97).

In multivariate smear-stratified analyses of all smear groups, age was significantly associated with infection. Having a college/university degree reduced infection risk in women with a current normal (OR 0.58, 95% CI 0.34–0.99) or BNA smear (OR 0.72, 95% CI 0.56–0.91) but not in those with a mild smear. In all smear strata, divorced/separated/widowed women had higher risk than married/co-habiting women (normal OR 1.64, 95% CI 0.91–2.96; BNA OR 2.26, 95% CI 1.73–2.95; mild OR 2.12, 95% CI 1.49–3.02). In the BNA strata only, being single also increased risk (OR 1.34, 95% CI 1.06–1.70). Having been pregnant was inversely associated with infection in those with a current normal (OR 0.60, 95% CI 0.38–0.95) or BNA smear (OR 0.81, 95% CI 0.64–1.02), but not in those with a mild smear. Having had children was associated with reduced risk in all smear strata, only reaching statistical significance in the current normal group (OR 0.57, 95% CI 0.36–0.92). Hormonal contraceptive use was associated with increased risk in the current normal (OR 1.59, 95% CI 1.02–2.48) and BNA (OR 1.29, 95% CI 1.05–1.59) strata, but not among the mild group. Barrier contraceptive use, caesarean delivery, smoking, physical activity and ethnicity were unrelated to infection in all strata.

**DISCUSSION**

Our study was large, population-based and nested in a pragmatic RCT within the UK national CSPs. Among study participants, the current BNA: mild smear ratio (1.8:1) was close to that reported for the CSP screening age group in 2004–2005 (1.9:1) (NHS Health and Social Care Information Centre, 2005; ISD Scotland, 2007), suggesting our results are likely to be generalisable to women with low-grade smears.

While TOMBOLA participation was 52% overall, it was lower among younger women and those resident in more deprived areas (TOMBOLA Group, 2006), groups with increased HPV prevalence in this and other studies (Tonon et al, 1999; Cuzick et al, 2003; Winer and Koutsky, 2004). Thus, our crude hrHPV prevalence is likely to somewhat underestimate true prevalence among women with low-grade smears.

The treatment of lesions, and possibly also the act of taking a smear, can potentially clear cervical HPV infection (Shapiro et al, 2003; Sarian et al, 2005). Thus, hrHPV prevalence may be artificially lowered in populations with extensive screening coverage, such as the UK. Our participants had no previous treatment for cervical lesions and 66% had their last smear ≥3 years before becoming eligible for TOMBOLA. Since hrHPV infection averages 8–14 months (Ho et al, 1998; Woodman et al, 2001), the effect of screening participation on our prevalence estimate is probably small.

A limitation of our study is that we did not collect information on numbers of sexual partners, age at first intercourse, etc, because of CSP guidelines (Duncan, 1997). Some factors we found to be associated with hrHPV infection may be markers of sexual behaviour. For example, smoking is associated with having had multiple sexual partners (Osler and Kjaer, 1996; Escobedo et al, 1997; Lam et al, 2001; Bellis et al, 2004; Jarvelaide, 2004), which is consistent with the observed raised infection risk among current smokers. UK rates of new partner acquisition vary by marital status, being highest among single or previously married women, intermediate among co-habiting women and lowest in married women (Johnson et al, 2001), a pattern compatible with our findings.

Our analyses extend existing knowledge on UK hrHPV prevalence, and are novel for Grampian and Tayside. Data from this and similar analyses will aid interpretation of studies of HPV testing, as well as for policy makers in defining HPV vaccination strategies. It also provides a baseline against which the impact of vaccination on HPV infection patterns can be assessed in the future.

**Smear status**

Other than age, current smear grade was the strongest predictor of infection. In women with a current BNA smear, our hrHPV prevalence (crude 34.2%, age-standardised 30.7%) was similar to that among women with a BNA smear from the UK ARTISTIC trial (31%) (Kitchener et al, 2006), but lower than (unstandardised) frequencies from other UK studies (46%; Moss et al, 2004, ~55%; Hibusitts et al, 2006, 72%; Cuscieri et al, 2004), and for women with ASCUS (atyypical cells of undetermined significance) smears from the US ALTS trial (49%; ALTS Group 2003). In the UK HART study, HPV prevalence among 289 women aged 30–60 years with a current BNA smear was 27% (Cuzick et al, 2003), close to the crude
## Table 1
Numbers and proportions of women hrHPV+ve and adjusted multivariate ORs for socio-demographic and lifestyle factors

|                           | Total (n) | hr HPV+ve (n) | % hrHPV+ve | Multivariate OR* | 95% CI      |
|---------------------------|-----------|---------------|------------|------------------|-------------|
| **Overall**               | 5038      | 1973          | 39.2       |                  |             |
| **Tertiary education/training** |           |               |            |                  |             |
| No degree                 | 4122      | 1656          | 40.2       | 1 Reference      |             |
| Degree                    | 887       | 305           | 34.4       | 0.72             | 0.61–0.87   |
| Missing                   | 29        | 12            | 41.4       |                  |             |
| **Global χ² = 12.85, P = 0.0003** |           |               |            |                  |             |
| **Ethnicity**             |           |               |            |                  |             |
| White                     | 4787      | 1868          | 39.0       | 1 Reference      |             |
| Other (non-white)         | 223       | 95            | 42.6       | 1.42             | 1.03–1.94   |
| Missing                   | 28        | 10            | 35.7       |                  |             |
| **Global χ² = 4.68, P = 0.0306** |           |               |            |                  |             |
| **Marital status**        |           |               |            |                  |             |
| Married/living as married | 2824      | 840           | 29.8       | 1 Reference      |             |
| Divorced/separated/widowed| 667       | 289           | 43.3       | 1.97             | 1.62–2.40   |
| Single                    | 1494      | 826           | 55.3       | 1.29             | 1.09–1.53   |
| Missing                   | 53        | 18            | 34.0       |                  |             |
| **Global χ² = 47.80, P < 0.0001** |           |               |            |                  |             |
| **Ever pregnant**         |           |               |            |                  |             |
| No                        | 1589      | 855           | 53.8       | 1 Reference      |             |
| Yes                       | 3412      | 1104          | 32.4       | 0.75             | 0.63–0.89   |
| Missing                   | 37        | 14            | 37.8       |                  |             |
| **Global χ² = 11.30, P = 0.0008** |           |               |            |                  |             |
| **Age at first pregnancy**|           |               |            |                  |             |
| Never pregnant            | 1589      | 855           | 53.8       | 1 Reference      |             |
| First pregnancy aged <20 years | 1080      | 453           | 41.9       | 0.86             | 0.71–1.05   |
| First pregnancy aged over 20 years | 2303      | 640           | 27.8       | 0.67             | 0.55–0.80   |
| Missing                   | 66        | 25            | 37.9       |                  |             |
| **Global χ² = 19.76, P = 0.0001** |           |               |            |                  |             |
| **Children**              |           |               |            |                  |             |
| No                        | 2113      | 1096          | 51.9       | 1 Reference      |             |
| Yes                       | 2869      | 854           | 29.8       | 0.71             | 0.60–0.83   |
| Missing                   | 56        | 23            | 41.1       |                  |             |
| **Global χ² = 17.06, P < 0.0001** |           |               |            |                  |             |
| **Number of children**    |           |               |            |                  |             |
| 1                         | 793       | 324           | 40.9       | 1 Reference      |             |
| 2                         | 1170      | 288           | 24.6       | 0.75             | 0.59–0.95   |
| 3                         | 563       | 148           | 26.3       | 0.89             | 0.67–1.19   |
| 4                         | 190       | 49            | 25.8       | 0.82             | 0.54–1.24   |
| 5–8                       | 86        | 25            | 29.1       | 1.11             | 0.64–1.94   |
| Missing                   | 67        | 20            | 29.9       |                  |             |
| **Global χ² = 7.23, P = 0.1242** |           |               |            |                  |             |
| **Caesarean ever**        |           |               |            |                  |             |
| No                        | 2367      | 704           | 29.7       | 1 Reference      |             |
| Yes                       | 481       | 145           | 30.2       | 1.12             | 0.88–1.43   |
| Missing                   | 21        | 5             | 23.8       |                  |             |
| **Global χ² = 0.85, P = 0.3574** |           |               |            |                  |             |
| **Reproductive history**  |           |               |            |                  |             |
| Never pregnant            | 1589      | 855           | 53.8       | 1 Reference      |             |
| First pregnancy < age 20 years, have children | 867       | 335           | 38.6       | 0.79             | 0.64–0.99   |
| First pregnancy < age 20 years, no children | 205       | 113           | 55.1       | 1.01             | 0.73–1.40   |
| First pregnancy ≥ age 20 years, have children | 1981      | 513           | 25.9       | 0.61             | 0.50–0.75   |
| First pregnancy ≥ age 20 years, no children | 313       | 125           | 39.9       | 0.83             | 0.62–1.10   |
| Missing                   | 83        | 32            | 38.6       |                  |             |
| **Global χ² = 25.55, P < 0.0001** |           |               |            |                  |             |
| **Current barrier contraception** |           |               |            |                  |             |
| No                        | 4211      | 1611          | 38.3       | 1 Reference      |             |
| Yes                       | 811       | 354           | 43.7       | 1.05             | 0.87–1.27   |
| Missing                   | 16        | 8             | 50.0       |                  |             |
| **Global χ² = 0.29, P = 0.5907** |           |               |            |                  |             |
prevalence among women ≥ 30 years in our study (26%). Our prevalence estimate among women with a current mild smear (crude 60.9%, age-standardised 52.7%) was also lower than non-standardised estimates from the United Kingdom and the United States of America of at least 70% (ALTS Group 2003; Moss et al., 2004; Hibbitts et al., 2006; Kitchener et al., 2006). In addition to different age profiles, comparison between studies is complicated by different HPV testing regimes (since tests detect different strains and vary in performance characteristics; Kulmala, 2004; Bosch and Iftner, 2005) and UK/USA differences in cytological abnormality classification.

Our crude (16.0%) and age-standardised (15.1%) prevalences among women with a current normal smear were similar to the pooled estimate from 27 PCR-based studies of cytologically normal women mainly from North America and Europe (16.2%) (Xi and Koutsky, 2004; Bosch and Iftner, 2005) and UK/USA differences in cytological abnormality classification.

Table 1 (Continued)

| Hormonal contraceptiona | Total (n) | hr HPV+ve (n) | % hrHPV+ve | Multivariate ORb | 95% CI      |
|-------------------------|----------|--------------|------------|-----------------|-------------|
| Never pill user/no other current hormonal contraception | 2416 | 649 | 26.9 | 1 | Reference |
| Never pill user/currently use other hormonal contraception | 200 | 101 | 50.5 | 1.58 | 1.06–1.66 |
| Ex-pill user/no other current hormonal contraception | 551 | 256 | 46.5 | 1.33 | 1.20–1.47 |
| Ex-pill user/currently use other hormonal contraception | 98 | 48 | 49.0 | 1.30 | 0.71–1.76 |
| Current pill | 1694 | 889 | 52.5 | 1.34 | 1.17–1.52 |
| Missing | 79 | 30 | 38.0 | 1 | Reference |

Global $\chi^2 = 27.33$, $P < 0.0001$

| Physical activityc | Total (n) | hr HPV+ve (n) | % hrHPV+ve | Multivariate ORd | 95% CI      |
|-------------------|----------|--------------|------------|-----------------|-------------|
| Never | 720 | 275 | 38.2 | 1 | Reference |
| Ever | 4239 | 1665 | 39.3 | 0.86 | 0.71–1.04 |
| Missing | 79 | 33 | 41.8 | 1 | Reference |

Global $\chi^2 = 2.40$, $P = 0.1216$

| Smoking status | Total (n) | hr HPV+ve (n) | % hrHPV+ve | Multivariate ORe | 95% CI      |
|----------------|----------|--------------|------------|-----------------|-------------|
| Never smoker | 2340 | 862 | 36.8 | 1 | Reference |
| Ex-smoker | 851 | 264 | 31.0 | 0.88 | 0.73–1.07 |
| Current smoker | 1798 | 822 | 45.7 | 1.21 | 1.04–1.40 |
| Missing | 49 | 25 | 51.0 | 1 | Reference |

Global $\chi^2 = 11.83$, $P = 0.0027$

Abbreviations: CI, confidence interval; hrHPV+ve, hrHPV positive; OR, odds ratio. aMultivariate OR adjusted for age/smear, tertiary education/training, ethnicity, marital status, reproductive history, use of hormonal contraception and smoking status. bMultivariate OR adjusted for age/smear, tertiary education/training, ethnicity, marital status, use of hormonal contraception and smoking status. cRestricted to women who have had children. dEver been pregnant, age at first pregnancy and ever had children were all individually associated with hrHPV. As these variables are related, a composite variable was created and fitted in model. eWomen were classified into one of five categories on the basis of current use of oral contraceptive pill or other hormonal contraception, and on any previous oral contraceptive pill use. fThere was no effect on risk of hrHPV of physical activity (never/ever) or of frequency of physical activity (data not shown).

Ethnic group

In the United Kingdom, white, black-African and black-Caribbean women have higher numbers of lifetime sexual partners, lower median age at first heterosexual intercourse and higher incidence of (non-HPV) sexually transmitted infections than women from Indian or Pakistani ethnic groups (Fenton et al., 2005). Although we observed increased infection risk among non-white ethnic groups, relatively few women described themselves thus ($n = 223$), precluding multivariate analysis of individual groups. Crude infection frequencies (Asian origin 35%; white 39%; black 45%) are consistent with sexual behaviour data and suggest that the raised risk may be limited to black women.

Contraception

High-risk HPV infection risk was > 50% higher in women who had used OCs or other hormonal contraceptives. The latter have been studied little previously. Among ALTS participants, no association was found with injectable contraceptives or Norplant (Castle et al., 2005). Previous studies of OC use have been inconsistent (Green et al., 2003; Winer and Koutsky, 2004; Vaccarella et al., 2006a), perhaps due to differences in study design, types of OCs used/assessed, prevalence of use and adjustment factors. While OC use may simply be a marker for ‘high-risk’ sexual behaviours (Winer and Koutsky, 2004), in several studies the OC–hrHPV association persisted after adjustment for factors such as number of sexual partners (Ley et al., 1991; Sikstrom et al., 1995; Winer et al., 2003). In further analyses, we found a stronger relationship between current, than past, OC use and hrHPV positivity (OR ex-users vs never users 1.23 (95% CI 0.99–1.51); OR current users vs never users 1.46 (95%...
Reproductive history

Our observation that having been pregnant was associated with reduced hrHPV infection risk is consistent with the IARC HPV Prevalence Surveys Study Group analysis of >15,000 women (Vaccarella et al, 2006a). We found that the effect was stronger if a childbirth had resulted, and with older age at first pregnancy. In the United Kingdom, earlier age at first pregnancy or childbirth, and decreased likelihood of having an abortion, are associated with low socio-economic status (Smith, 1993; Wellings et al, 2001; ISD Scotland, 2006). However, our analysis was adjusted for tertiary education as a measure of socio-economic status. Although age at first pregnancy may be a marker for age at sexual debut, it is not as strongly protective as HPV infection as previously thought (Vaccarella et al, 2006b). Possible explanations for this inverse association with pregnancy include breastfeeding, which results in high progesterone levels with atrophic changes and retraction of the squamocolumnar junction into the cervical canal, possibly reducing the likelihood of infection; alterations in patterns of sexual (e.g. changing partners, frequency of coitus) and other behaviours that influence infection risk (e.g. smoking).

Age- and smear-stratified analyses

Identifying differences in the relative importance of risk factors in sub-groups can be informative – as is evident from the few previous studies using this analytical approach (Lazcano-Ponce et al, 2001; Molano et al, 2002; Anh et al, 2003). We undertook age- and smear-stratified analyses because these were the most important risk factors, and they interacted, suggesting that the relative contribution of hrHPV infection, and other factors, in the aetiology of cytological abnormalities differs by age.

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