

## Letter to the Editor

## Reply: Breast cancer, human papilloma virus and sexual activities

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There are now five studies, including the report of Akil and co-workers in this issue of the *Br J Cancer*, for which the relationship between age of women and high-risk human papilloma virus (HPV)-positive breast cancer, has been published. Three of these studies report that the age of women with HPV-positive breast cancer is significantly younger than the women with HPV-negative breast cancer. On an average, Greek women with HPV-positive breast cancer were 15 years, Australian women 8 years, and Canadian and Syrian women were 11 years younger than those with HPV-negative breast cancer (Kroupis *et al*, 2006; Lawson *et al*, 2006; Akil *et al*, 2007). Two studies report no difference in the age of women with HPV-positive or -negative breast cancer (Hennig *et al*, 1999; Damin *et al*, 2004). Some details of these studies are shown in Table 1.

Based on the younger age of some women with HPV-positive breast cancer, and the higher incidence of HPV-positive cervical cancer among younger women with multiple sexual partners, we have hypothesised that high-risk HPVs may be transmitted to the breast during sexual activities (Lawson *et al*, 2006).

The underlying assumption to these observations and hypotheses is that high-risk HPVs may have a causal role in some breast cancers. Therefore, a brief overview of the relevant evidence is of value.

The presence of high-risk HPV DNA in breast tumours has been shown, mainly by PCR analyses, in 11 out of 13 studies conducted in a various countries (reviewed by Lawson *et al*, 2006; plus a recent positive study by Yasmeen *et al*, 2007; a negative study by Lindel *et al*, 2007). Tumours of the breast nipple appear to have histological characteristics similar to HPV-positive cervical cancer (de Villiers *et al*, 2005).

Similar high-risk HPVs have been identified in breast tumours and cervical cancer that have occurred in the same women (Hennig *et al*, 1999; Widschwendter *et al*, 2004).

There is immortalisation and preneoplastic transformation of normal breast epithelial cells by HPVs (Band, 1995).

High-risk HPVs, in particular HPV types 16, 18, 31, 33 and less commonly additional types, are the accepted cause of cervical and other ano-genital cancers (IARC, 1995). Less well known is the likely causal role of high-risk HPVs in cancers of the head and neck (van Houten *et al*, 2001). The biological mechanisms by which HPVs are tropic and oncogenic to epithelial cells is reasonably well known from studies of cervical oncogenesis. These mechanisms include the presence and genomic integration of HPV DNA in epithelial tumours, the expression of the HPV E6 oncogene in the tumour where it binds to and degenerates the tumour suppressor p53 gene allowing unregulated cell proliferation to occur (zur Hausen, 2002). Hormones play a central role on HPV oncogenesis. Estrogens synergise with HPV oncogenes to cause cervical cancer (Brake and Lambert, 2005) and the regulatory region of HPV 16 contains DNA sequences that are responsive to glucocorticoid hormones (Gloss *et al*, 1987).

Because of the presumably low viral load, PCR analyses for HPV on both formalin-fixed and fresh-frozen breast tumour specimens are difficult and very dependent on the details of the methods used. For example, the negative outcomes by Lindel *et al* (2007) have probably been because they used the incorrect PCR primers (Damin *et al*, 2007; Yasmeen *et al*, 2007). In our own studies, the identification of HPV DNA proved to be difficult and required additional amplification of the DNA before PCR and the use of SYBR Green I to optimise detection (Kan *et al*, 2005).

**Table 1** Average age of women with HPV-positive and HPV-negative breast cancer

Study	Population	HPV type	Age HPV +	Age HPV–	P-Value for age difference
Hennig <i>et al</i> , 1999; n = 107	Norway	16	50.8	49.4	0.659, NS
Damin <i>et al</i> , 2004; n = 101	Brazil	16/18	56.5	55.9	0.806, NS
Kroupis <i>et al</i> , 2006; n = 107	Greece	16	38	55	0.001, S
Lawson <i>et al</i> , 2006; n = 50	Australia	18	55.6	63.8	0.049, S
Akil <i>et al</i> , 2007	Canada/Syria	16	46.5	57.5	0.05, S

NS = not significant; S = significant at 95% level.

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The main means of transmission of HPVs appears to be by surface contact. The human papilloma virions are released when the cornified envelope of cells desquamate (Bryan and Brown, 2001). The possibility of transmission of high-risk HPVs during sexual activity is demonstrated by the high prevalence of these viruses in male and female genital organs. The prevalence of high-risk HPVs in male genital organs varies by population and methods of detection. The prevalence of high-risk HPVs in the penile glans, penile shaft, prepuce and scrotum is between 5 and 50%, the perianal area 0–33%, semen 2–83% and urine up to 7% (Dunne *et al*, 2006). High-risk HPVs are also present in normal, benign hyperplastic and malignant prostate tissues (Zambrano *et al*, 2002). The prevalence of high-risk HPVs in

females varies between populations and dramatically so between age groups, with the prevalence in near normal cervical smears from UK women 61% at ages 20–24 decreasing to 14–15% in those over 50 years (Cotton *et al*, 2007).

What meaning might be given to these observations? In our view, the evidence that high-risk HPVs may have an aetiological role in human breast cancer is substantial but far from conclusive. Obviously further work needs to be done.

A working hypothesis is that high-risk HPVs may be involved in the initiation of breast cancer among younger women.

**The Editor now considers correspondence on this publication closed.**

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