Commentary
DOI 10.1007/s12038-010-0038-y

Human papillomavirus and tar hypothesis for squamous cell cervical cancer

Cervical cancer is the second most common life-threatening cancer among women worldwide, with incidence rates ranging from 4.8 per 100,000 in the Middle East to 44.3 per 100,000 in East Africa. Human papillomavirus (HPV) infection, especially HPV-16 and HPV-18, plays a major role in the etiology of cervical cancer, but HPV alone is not sufficient to induce cancer. We propose that squamous cell cervical cancer is caused by an interaction of oncogenic viruses and cervical tar exposures. Cervical tar exposures occur from cigarette smoking, use of tar-based vaginal douche products (TBD), and long years of inhaling smoke from wood- and coal-burning stoves in poorly ventilated kitchens.

1. Introduction

We will review data for four factors associated with the etiology of cervical cancer and discuss how they might interact to induce cancer. HPV and tobacco smoke are acknowledged by international agencies as causative for cervical cancer. In 1995, a World Health Organization consensus panel concluded that "at least" HPV-16 and HPV-18 caused cervical cancer (Anonymous 1995). In 2004, the International Agency for Research on Cancer (IARC) classified tobacco smoking as another cause of cervical cancer (Anonymous 2004). Two other factors, exposure to tar-based vaginal douche products and to the smoke generated by wood- and coal-burning stoves might also serve as etiologic factors in cervical cancer. In this paper, we will review the data linking all four factors, but concentrate on the two less appreciated factors, and discuss our rationale for our virus-tar hypothesis.

2. Human papillomaviruses

In 2008 Harald zur Hausen won the Nobel Prize in Medicine for his work linking HPV to cervical cancer (zur Hausen, 1989). HPV is the most important risk factor for developing cervical cancer. Persistent infection with a high risk "oncogenic" type of HPV is essential for the development of invasive cervical cancer (Walboomers *et al*. 1999; Munoz *et al.* 2003). In other words, HPV may be necessary but is not sufficient to cause cervical cancer.

Cancer of the cervix is a leading cause of cancer-related deaths in women worldwide, especially among women in underdeveloped countries. Worldwide, approximately 500,000 cases of cervical cancer are diagnosed each year. The highest rates of cervical cancer occur in sub-Saharan Africa, where the annual incidence surpasses 40 per 100,000. Routine screening is one approach that contributes to the decreasing incidence of invasive cervical cancer in the United States, where approximately 13,000 cases of invasive cervical cancer and 50,000 cases of cervical carcinoma *in situ* are diagnosed yearly. In the USA, invasive cervical cancer is more common among middle-aged and older women, African-American, Hispanic and Native American women, and among women of lower socioeconomic status. Such women are less likely to receive regular screening and early treatment (Haverkos 2005; Jemal *et al*. 2008).

There is a strong association between human papillomavirus infection and cervical cancer. HPV is a common sexually transmitted disease. However, most women who become infected with HPV will not

Keywords. Cervical cancer; co-factors; human papillomavirus; tar-based vaginal douche; tobacco smoke; wood smoke

develop cervical cancer. There are more than 100 different strains of HPV, approximately 20 of which are associated with cervical cancer (i.e. HPV 16, 18, 31, etc.) (Bosch *et al*. 1995; Munoz *et al*. 2003). We propose that several tar-based factors may contribute to the development of cervical cancer.

3. How cigarette smoking might interact with HPV and induce cancer

Cigarette smoke is another carcinogen associated with cervical cancer. In 1977 Warren Winkelstein was the first to suggest that cigarette smoking might be a causative factor for cervical cancer. He reviewed surveillance data in the USA and noted a correlation between age-adjusted incidence rates for cervical cancer and male lung cancer (Winkelstein *et al*. 1977). He also noted that smoking was a risk factor for cervical cancer in four case-control studies (Winkelstein 1977).

Since 1977 several investigators have confirmed Winkelstein's epidemiologic findings in Asia, Europe and the USA. Current smokers and former smokers had increased risk of squamous cell cervical cancer compared to never smokers (Castle *et al*. 2002; Haverkos *et al.* 2003; International Collaboration of Epidemiological Studies of Cervical Cancer 2006). In an ecologic analysis, researchers correlated cigarette smoking prevalence with cervical cancer rates in over 70 countries worldwide and found a positive correlation between smoking and cervical cancer in the USA and Europe, but not worldwide (Steckley *et al*. 2003). In 2004, the International Agency for Research on Cancer (IARC) classified tobacco smoking as a cause of cervical cancer (Anonymous 2004). Chemicals in cigarette smoke may reach the cervix thorough the blood, where they are purported to incorporate into DNA of cervical cells and disrupt normal cell regulation (Prokopczyk *et al.* 1997, 2008). Toxins from cigarettes may directly impair the immune defence of cervical epithelial tissue.

Tobacco smoke is known to contain over 4000 compounds, including benzyl (a) pyrenes, polycyclic aromatic compounds, and tobacco specific nitrosamines, such as 4-(methylnitroamino)-1-(3-pyridyl)-1-butanone (NNK). Two of those compounds, namely cotinine and NNK have been identified at higher levels in the cervical mucous of smokers than non-smokers (Prokopczyk *et al*. 1997). There is laboratory evidence that HPV and NNK found in tobacco smoke may interact and produce changes in human cells. Prokopczyk and colleagues have treated HPV-16-immortalized human ectocervical cells with three different doses of NNK for 12 weeks, and observed alterations of genes involved in cellular transformation. These results support the biological plausibility that a tobacco specific compound can be transported to the cervix through the blood and alter HPV infected cells *in vitro* (Prokopczyk *et al.* 2008).

4. Tar-based vaginal douche products and cervical cancer

Tar-based vaginal douche products (TBD) were associated with the development of cervical cancer in the mid-twentieth century resulting in the voluntary removal of TBD from US markets. The role for TBD in cervical cancer was first suggested in 1931 by Dr Frank Smith, a New York City obstetrician-gynecologist, who noted that the use of Lysol® douches was significantly more frequent among his patients with cervical cancer than among his other patients. Smith conducted a case-control study interviewing 226 of his cervical cancer patients at the Gynecological Service of Memorial Hospital and 202 women as controls. One-hundred three (49%) of cervical cancer patients used Lysol® douche compared with 37 (18%) of controls (we calculate Odds Ratio = 3.7); 41 (19%) of cases used no vaginal douche compared with 58 (29%) of controls (Table VII of Smith 1931). Smith described Lysol® as a coal-tar soap containing cresol from beech-tar distillation, and noted that tars and oils were universally employed in experimental models of cancer (Smith, 1931). In 1950, epidemiologists Lombard and Potter compared behavioral characteristics of 523 women with cervical cancer with 6 different sets of control women. They reported that 'long-continued' douching with coal tar derivatives, such as lysol, creolin, sulfonaphthol, and carbolic acid, was reported more frequently by patients (31%) with cervical cancer than among controls (13-20%); and the difference remained significant in multi-variant analyses (Lombard and Potter 1950). In 1967, Rotkin reported the results of a case-control study in which 416 California women with cervical cancer were compared with hospital-based controls matched for age, race, religion, and hospital. Rotkin found a significant association with usage of an unnamed commercial vaginal douche product and cervical cancer.

Ninety-two percent of cases douched compared with 83% of controls (Chi-square = 15.06, P <0.0001); 52% of cases used a popular advertised coal tar derived douche compared to 40% of controls (P = 0.001) (Rotkin 1967). Results of these three investigations led to the voluntary removal of Lysol® and other tar-based vaginal douche products from the US market in 1970.

To further evaluate the association of TBD and cervical cancer, one of us (HH), working with National Cancer Institute (NCI) and Food and Drug Administration (FDA), compiled a list of 24 tar-based organic chemicals used in vaginal douche products in the US between 1930 and 1970. They investigated whether those chemicals had properties consistent with induction of tissue inflammation and/or carcinogenicity. They identified several tar-based constituents of such products as chemical irritants and/or possible carcinogens that may be implicated as cofactors with HPV in the etiology of cervical cancer (Haverkos *et al*. 2008)

5. Wood burning stoves and cervical cancer

In 2000, Dutch and Central American investigators compared lifestyle factors between 99 women in Honduras with cervical cancer and 199 age and clinic-matched controls. Not surprisingly HPV was strongly associated with cervical cancer (Odds Ratio equals 7.66, 95% CI: 3.88-15.1). We calculate the proportion of attributable risk for HPV-DNA as 75%. Among HPV-positive women, significant relationships were observed for education, age at first intercourse, and, surprisingly, exposure to wood smoke. Among women with 25-34 years of exposure to wood smoke, the Odds Ratio was 3.67, 95% CI: 1.48-9.09; and for women with greater than 35 years of exposure, the Old Ratio was 6.35, 95% CI: 2.10-19.29 (Ferrera *et al.* 2000). We calculate the proportion of attributable risk for wood smoke exposure greater than 25 years as 25%

If cigarette smoke is a causal factor for cervical cancer, why not wood smoke? Wood smoke contains a similar spectrum of carcinogens, such as polycyclic aromatic hydrocarbons, sulphur and nitrogen oxides. In 2002, the same investigators reported similar findings comparing 125 women with cervical intraepithelial neoplasia, CIN-1, CIN-2, and CIN-3, with 241 age- and clinic matched controls (Velema *et al*. 2002). More research is needed to explore those observations.

The World Health Organization collects data on solid fuel use by country. Worldwide, three billion people depend on wood, dung, coal, or crop residues for cooking and heating. The highest proportions of populations using solid fuels include several African countries, also those with the highest rates of cervical cancer (WHO, 2006). Exposure to environmental smoke may be the most important tar-based carcinogen exposure of women worldwide, and might explain the association of cervical cancer with lower socioeconomic status, and the geographic variability of cervical cancer.

To explore the relationship between solid fuel use and cervical cancer, we added WHO data regarding solid fuel use by country to that collected in another ecologic study of cervical cancer (Steckley *et al* 2003; WHO 2006) (see table1). Pearson correlation coefficient for cervical cancer and solid fuel use was 0.498 (P < 0.05).

6. Discussion

Although there may be several ways to interpret these data, we believe that they are consistent with a multifactorial hypothesis. HPV appears to be necessary but not sufficient to induce cervical cancer. The WHO acknowledges tobacco smoking as a causative factor. Laboratory data support at least one tobacco carcinogen, NNK, can be found at higher levels in the cervix of smokers and alter gene expression of HPV-infected cells

In the 20th century, Peyton Rous (1879-1970) and others proposed multifactorial causes of cancers and other diseases. Rous and colleagues demonstrated the joint action of methylcholanthrene, a polycyclic aromatic hydrocarbon, and Shope papillomavirus to consistently induce squamous cell carcinomas in rabbits. These historic experiments were among the first to induce cancer in animals through co-carcinogenesis, and led to the concept of “initiation and promotion” as an etiology for cancer (Rogers and Rous 1951). Using the Rous rabbit model as a prototype, one might hypothesize that some, if not all

Table 1. Cervical cancer, smoking rates, solid fuel use, and gross domestic product per capita by country (*N*=73)

Country	Cervical cancer per 100,000 (rank)	Percent female smokers (rank)	Percent solid fuel use (rank)	GDP per capita (rank)
Zambia	61.08 (1)	10.0 (54)	87 (2)	880 (73)
Swaziland	52.16 (2)	2.1 (69)	64 (12)	4,200 (49)
Zimbabwe	52.09 (3)	1.2 (71)	72 (7)	2,400 (61)
Lesotho	45.75 (4)	1.0 (72)	83 (3)	2,400 (61)
Ecuador	44.18 (5)	18.3 (37)	< 5 (35)	4,800 (46)
Guatemala	44.00 (6)	17.7 (40)	62 (13)	3,800 (55)
Paraguay	41.10 (7)	5.5 (6.2)	53 (15)	3,700 (56)
El Salvador	40.56 (8)	12.0 (50)	33 (19)	3,000 (59)
Mexico	40.49 (9)	18.4 (35)	14 (29)	8,300 (35)
Peru	39.95 (10)	15.4 (43)	33 (19)	4,300 (48)
Dominican Republic	38.41 (11)	17.1 (42)	15 (28)	5,000 (44)
Venezuela	38.33 (12)	39.2 (1)	5 (34)	8,300 (34)
Honduras	36.65 (13)	11.0 (52)	57 (14)	2,400 (61)
Samoa	32.86 (14)	24.0 (22)	70 (9)	2,100 (66)
Romania	31.50 (15)	15.2 (45)	23 (22)	4,050 (53)
Brazil	31.26 (16)	29.3 (10)	13 (30)	6,100 (42)
Panama	31.23 (17)	20.0 (31)	33 (19)	7,300 (38)
Chile	29.15 (18)	18.3 (37)	< 5 (35)	12,500 (28)
South Africa	28.86 (19)	11.0 (52)	18 (25)	6,800 (39)
Bangladesh	27.64 (20)	10.0 (54)	89 (1)	1,380 (70)
Nepal	26.47 (21)	15.4 (44)	81 (4)	1,100 (72)
Mauritius	26.46 (22)	3.3 (67)	< 5 (35)	10,000 (32)
Costa Rica	24.96 (23)	6.6 (59)	23 (22)	6,700 (41)
Namibia	24.70 (24)	35.0 (2)	65 (11)	4,100 (50)
Cuba	23.85 (25)	26.3 (18)	21 (24)	1,560 (69)
Algeria	23.39 (26)	6.6 (59)	< 5 (35)	4,600 (47)
Philippines	22.66 (27)	18.0 (39)	45 (18)	3,500 (58)
Bahamas	22.06 (28)	4.0 (65)	< 5 (35)	20,100 (19)
Hungary	22.05 (29)	27.0 (15)	< 5 (35)	7,400 (37)
Poland	21.05 (30)	19.0 (32)	< 5 (35)	6,800 (39)
Bulgaria	20.94 (31)	23.8 (24)	17 (26)	4,100 (50)
Denmark	19.02 (32)	30.0 (6)	< 5 (35)	23,300 (7)
Slovenia	18.88 (33)	20.3 (30)	8 (33)	10,300 (30)
Mongolia	17.97 (34)	19.0 (32)	51 (16)	2,250 (65)
Albania	17.78 (35)	6.3 (61)	50 (17)	1,490 (71)
Vietnam	17.57 (36)	4.3 (64)	70 (9)	1,770 (68)
Slovakia	16.59 (37)	30.0 (6)	< 5 (35)	8.300 (35)
Lithuania	16.06 (38)	8.6 (57)	< 5 (35)	4.900 (45)
Estonia	15.52 (39)	21.7 (29)	16 (27)	5,500 (43)
Czech Republic	15.09 (40)	12.0 (50)	< 5 (35)	11,300 (29)
Singapore	14.89 (41)	3.1 (68)	< 5 (35)	26,300 (4)
Portugal	14.60 (42)	7.1 (58)	< 5 (35)	14,600 (25)

Table 1. *(Continued)*

Argentina	14.16 (43)	34.0 (3)	< 5 (35)	10,300 (30)
Uruguay	13.85 (44)	14.3 (48)	< 5 (35)	8,600 (33)
Russian Federation	13.58 (45)	14.0 (48)	9 (32)	4,000 (54)
Norway	12.60 (46)	32.3 (4)	< 5 (35)	24,700 (5)
Austria	11.90 (47)	19.0 (32)	< 5 (35)	22,700 (9)
Germany	11.53 (48)	30.0 (6)	< 5 (35)	22,100 (15)
Japan	11.11 (49)	13.4 (49)	< 5 (35)	23,100 (8)
New Zealand	10.61 (50)	24.0 (22)	< 5 (35)	17,000 (23)
Iceland	10.41 (51)	28.0 (11)	< 5 (35)	22,400 (12)
France	10.14 (52)	27.0 (15)	< 5 (35)	22,600 (11)
Sweden	9.35 (53)	22.3 (27)	< 5 (35)	19,700 (20)
United Kingdom	9.34 (54)	28.0 (11)	< 5 (35)	21,200 (16)
Latvia	9.25 (55)	18.4 (35)	10 (31)	4,100 (50)
Belgium	9.09 (56)	26.0 (19)	< 5 (35)	23,400 (6)
Italy	9.05 (57)	17.3 (41)	< 5 (35)	20,800 (18)
Uzbekistan	8.31 (58)	1.0 (72)	72 (7)	2,500 (60)
Canada	8.25 (59)	23.0 (26)	< 5 (35)	22,400 (12)
Ireland	7.87 (60)	31.0 (5)	< 5 (35)	18,600 (21)
USA	7.84 (61)	22.1 (28)	< 5 (35)	31,500 (2)
Netherlands	7.28 (62)	30.6 (6)	< 5 (35)	22,200 (14)
Switzerland	7.23 (63)	27.4 (14)	< 5 (35)	26,400 (3)
Spain	7.20 (64)	24.7 (21)	< 5 (35)	16,500 (24)
Australia	7.14 (65)	23.2 (25)	< 5 (35)	21,200 (16)
Greece	6.92 (66)	28.0 (11)	< 5 (35)	13,400 (26)
Pakistan	6.47 (67)	9.0 (56)	81 (4)	2,000 (67)
Kuwait	5.78 (68)	1.9 (70)	< 5 (35)	22,700 (9)
Israel	5.76 (69)	25.0 (20)	< 5 (35)	18,100 (22)
Malta	5.65 (70)	14.6 (46)	< 5 (35)	13,000 (27)
China	5.24 (71)	3.8 (66)	80 (6)	3,600 (57)
Luxembourg	3.58 (72)	27.0 (15)	< 5 (35)	32,700 (1)
Iraq	3.27 (73)	5.0 (63)	< 5 (35)	2,400 (61)

Modified from Steckley *et al*. 2003.

cases of squamous cell cervical cancer, arise from an interaction between oncogenic viruses and cervical tar exposures. We welcome inquiries from laboratories interested in re-enacting the Rous rabbit model substituting tar-based chemicals identified in our review for methylcholanthrene in combination with exposure to Shope papillomavirus.

What can we tell women who cannot benefit from the new HPV vaccines in order to prevent cervical cancer? Furthermore, what can we tell women of developing nations who cannot afford the vaccine, have poor access to health care and cervical cancer screening, have limited cooking fuel options, and ready access to tobacco and tar-based douche products? If our hypothesis has merit, one could recommend specific lifestyle changes that might lessen one's risk for cervical cancer. First, women should be encouraged not to start smoking cigarettes and to avoid exposures to second-hand smoke. Women who smoke should be counseled to stop smoking and to be given the most effective therapies to aid smoking cessation. Second, women should be told that tar-based douching may be a risk factor for cervical cancer. Gynecologists should be aware of the chemical contents of the douche products their patients are using,

and discourage the use of tar-based products. Although tar-based products have been voluntarily removed from US markets, they are available in several countries worldwide. Finally, women should be told of the risks associated with inhaling wood and coal smoke in poorly ventilated areas and counseled about alternate cooking sources. Improving the environmental conditions that generate indoor pollutants in the developing world may have a more immediate impact on the incidence of cervical cancer as HPV vaccines are further developed and distributed worldwide. Given both the highest prevalence of cervical cancer and wood-burning in developing countries, this risk factor deserves further study.

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*e*Publication: 9 August 2010