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Multifactorial Etiology of Cervical Cancer: A Hypothesis

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Abstract

Cancer of the cervix is the second most common life-threatening cancer among women worldwide, with incidence rates ranging from 4.8 per 100,000 women per year in the Middle East to 44.3 per 100,000 in East Africa. Epidemiologic and clinical data demonstrate that human papillomaviruses (HPV), especially HPV-16 and HPV-18, play at least a major if not a necessary role in the etiology of cervical cancer. However, many investigators acknowledge that HPV is not sufficient to induce cervical cancer and that a multifactorial etiology is likely. HPV can be found in a growing proportion of patients with cervical cancer, approaching 100%, but is not yet found in every patient with disease. Other factors, such as herpes simplex virus type 2 infections, cigarette smoking, vaginal douching, nutrition, and use of oral contraceptives, have been proposed as contributing factors. In the first half of the 20th century, Peyton Rous and colleagues demonstrated the joint action of tars and Shope papillomavirus to consistently induce squamous cell carcinomas in rabbits. Using the Rous model as a prototype, one might hypothesize that some cases of cervical cancer arise from an interaction between oncogenic viruses and cervical tar exposures. Cervical tar exposures include cigarette smoking, use of tar-based vaginal douches, and long years of inhaling smoke from wood- and coal-burning stoves in poorly ventilated kitchens.

Background

Epidemiologic and clinical data indicate that HPV, especially HPV-16 and HPV-18, play a major role in the etiology of cervical cancer.[1] Expression of HPV-specific oncoproteins, E6 and E7, are considered essential in maintaining malignant growth of cervical cancer cells.[2] However, HPV infections are widespread in the general population yet cannot be found in every patient with cervical cancer, nor do all infections with HPV result in cervical cancer. There are many investigators who argue that HPV is a necessary etiologic factor, but few who maintain that it alone is sufficient to cause cervical cancer.[3-12]

Let me propose that the etiology of squamous cell cervical cancer results from a malignant interaction between oncogenic viruses, namely HPV and/or HSV-2, and cervical tar exposure(s) through chronic inhalation of wood smoke, smoking cigarettes, and/or use of tar-based vaginal douches (**Figure 1**). This multifactorial hypothesis was developed by identifying a biologically plausible pattern after review of clinical and epidemiologic studies and a preclinical model of cancer developed over 50 years ago by Peyton Rous and his colleagues.[13-15]

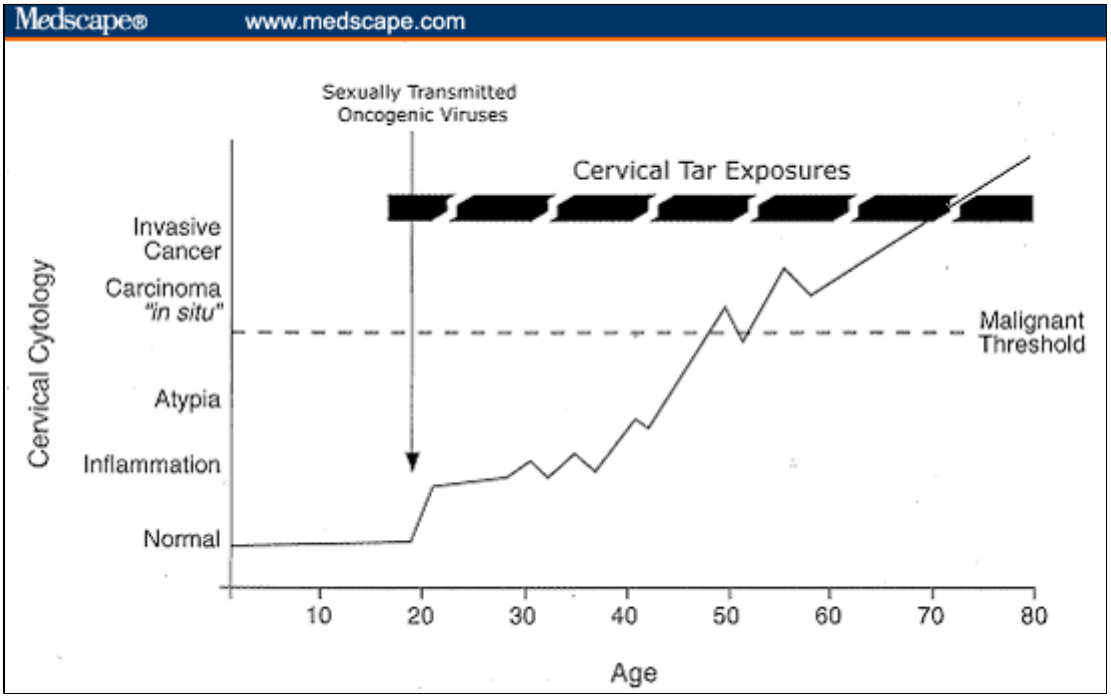

Figure 1.

Etiology of cervical cancer: an interactive hypothesis.

In 1966, after the first human cancers were attributed to viruses, Peyton Rous received the Nobel Prize in Physiology and Medicine for work he had done 50 years earlier. In 1911, Rous described a sarcoma that could be transmitted from chicken to chicken by inoculating a cell-free filtrate, later identified as the Rous sarcoma virus.[16,17] Subsequently, Rous and colleagues demonstrated the joint actions of tars, methylcholanthrene and benzathracene, and Shope papillomavirus to consistently induce squamous cell carcinomas in rabbits.[13-15] These historic experiments were among the first to induce cancer in animals through co-carcinogenesis.

Cancer of the uterine cervix is the second most common life-threatening cancer among women worldwide, second only to breast cancer. Incidence of cervical cancer varies by region of the world, ranging from 4.8 per 100,000 in Western Asia (ie, 3.27/100,000 in Iraq and 5.76/100,000 in Israel) to 44.3 in Eastern Africa (ie, 61.08/100,000 in Zambia and 52.16/100,000 in Swaziland) (Table).[18,19] In 2002, approximately 493,000 new cases of cervical cancer were diagnosed worldwide. That same year, 274,000 deaths were attributed to cervical cancer.[20]

Deaths from cervical cancer in the United States have declined in the last century. In 1930, the US Public Health Service started collating death certificate data from a subset of states. Age-adjusted cancer death rates for females, 1930-2000, are shown in **Figure 2**.[21] Note that uterine cancer rates are for uterine cervix and uterine corpus combined. It was not until 1973 that the National Cancer Institute recorded cervical cancer rates separately from uterine cancer rates and identified patients by race/ethnicity in the Surveillance, Epidemiology and End Results (SEER) registry (**Figure 3**).[22]

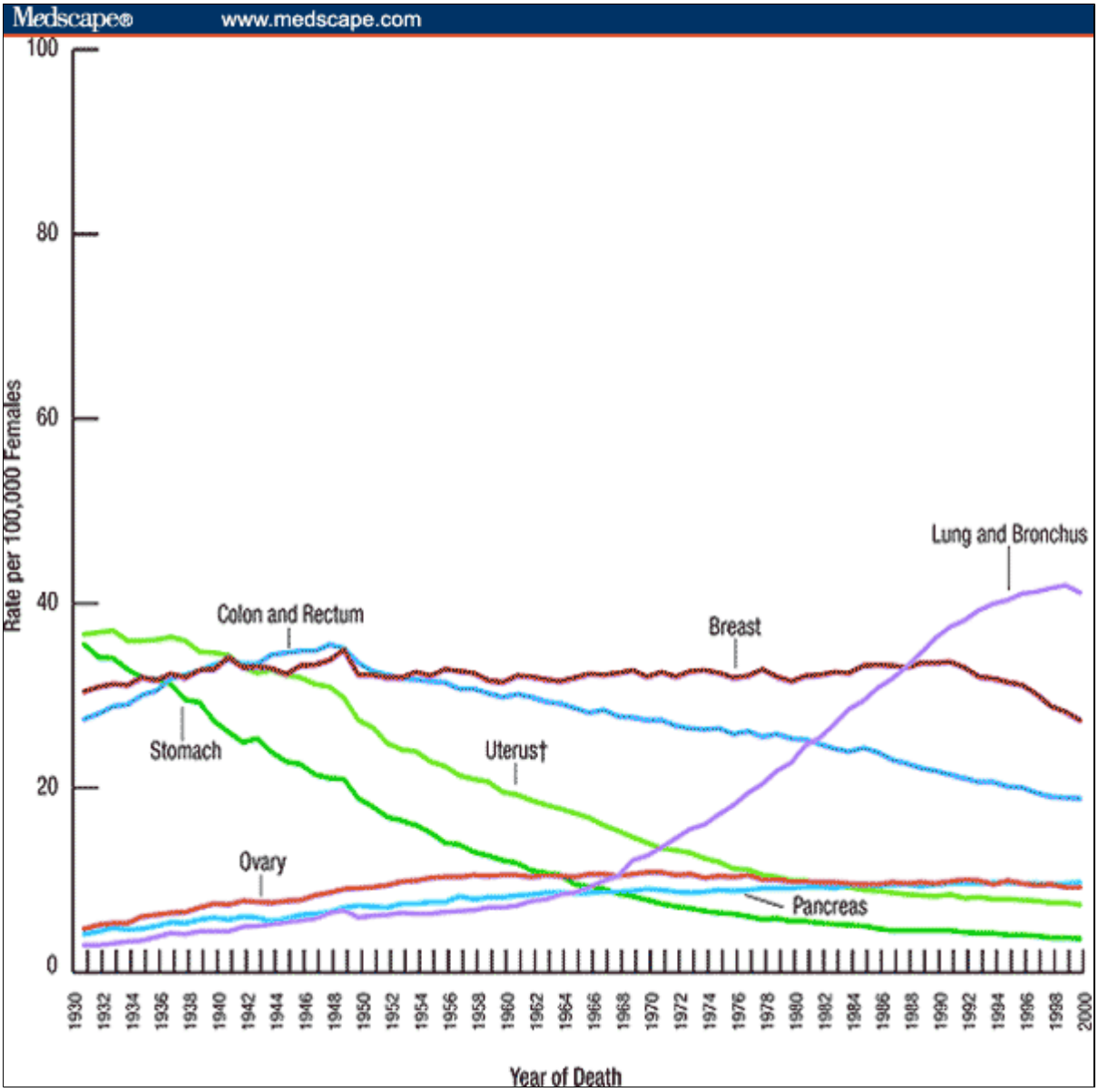

Figure 2.

Age-adjusted cancer death rates, females by site, United States, 1930-2000.*

*Uterus cancer death rates are for uterine cervix and uterine corpus combined.

Source: US Mortality Public Use Data Tapes 1960-2000, US Mortality Volumes 1930-1959, National Center for Health Statistics, CDC, 2003.

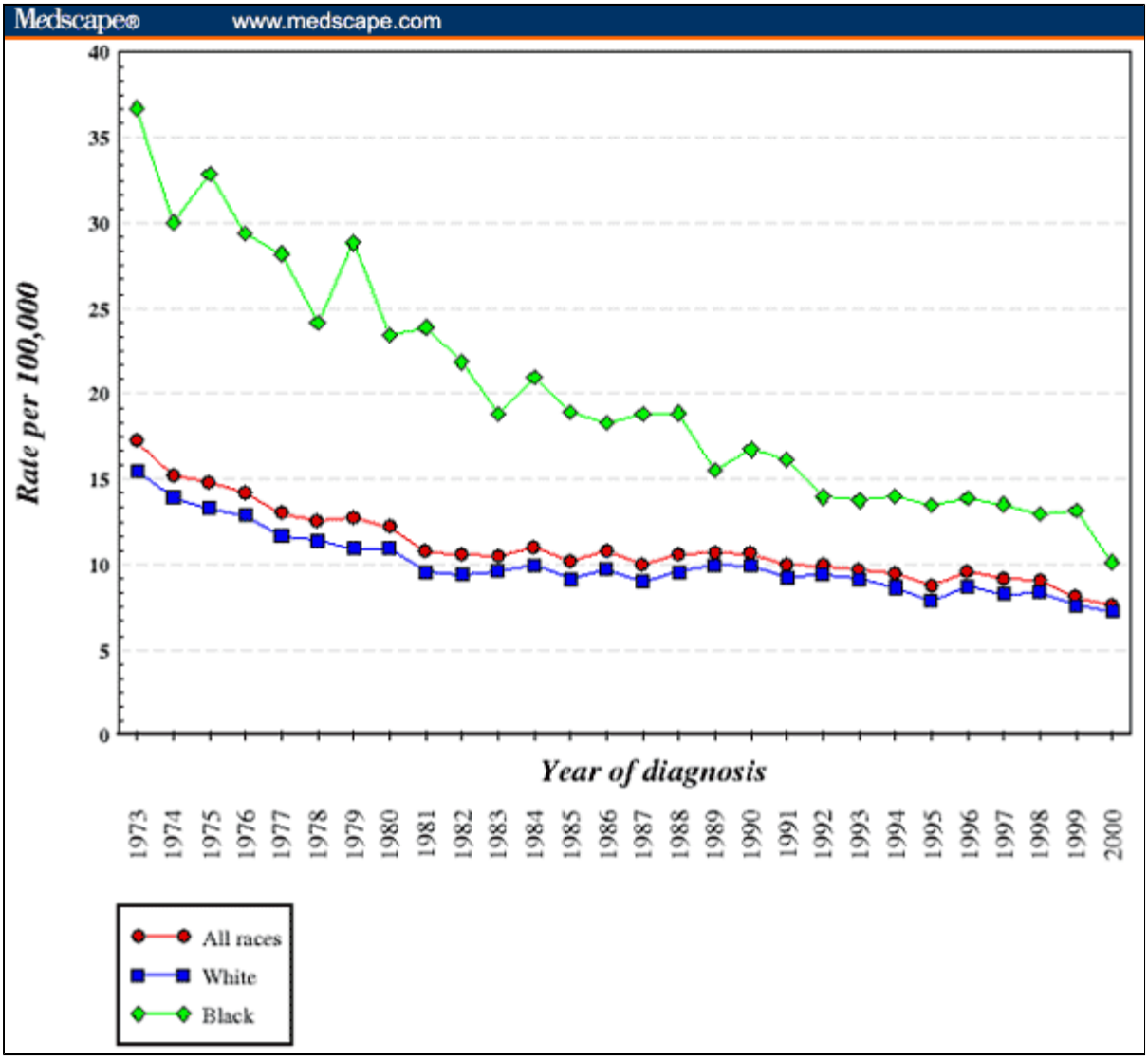

Figure 3.

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Public-Use, (1973-2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch.

Risk Factors -- Oncogenic Viruses

In 1842, Italian investigators reported little to no cervical cancer among Catholic nuns compared with the rest of the Italian female population.[23] Since then, epidemiologists have reported measures of sexual behavior associated with cervical cancer incidence including marital status, parity, age at first intercourse, numbers of male sex partners, and commercial sex work.[24] These findings led to a search for a sexually transmitted agent as the cause of cervical cancer and theories implicating syphilis, gonorrhea, herpes viruses, and, ultimately, human papillomaviruses (HPV).

In the 1970s, Harald zur Hausen postulated a role for, and then found HPV-DNA in cervical cancers.[25-28] In the 1980s, his group was the first to isolate HPV-16 and HPV-18 from cervical cancer tissues.[29,30] Several epidemiologists have subsequently shown highly statistically significant associations between HPV and development of cervical intraepithelial neoplasia (CIN) grade 2 or 3,[31] with persistent CIN 2[32] and with development of cervical cancer.[33,34] In 1995, a World Health Organization consensus panel gathered a large body of biologic and epidemiologic data and concluded that "at least" HPV-16 and HPV-18 infection caused cervical cancer.[1] HPV can be found in 90%-95% of patients with cervical cancer worldwide, most frequently HPV-16 (50%), HPV-18 (12%), HPV-45 (8%), and HPV-31 (5%).[35] However, HPV is a common infection among sexually active young women, such as college students.[36-38] For example, there was a 43% 3-year incidence of HPV infection among sexually active co-eds at Brown University.[37]

Harald zur Hausen was also the first to recognize that HPV was not sufficient for cancer induction, and proposed that herpes simplex

virus type 2 (HSV-2) and HPV act synergistically to induce cervical cancer.[39] Others have postulated a role for HSV-2 infection in the etiology of cervical cancer, while acknowledging the primary role for HPV.[40,41] For example, Hildesheim and colleagues[40] studied women with invasive cervical cancer in Latin America and compared viral and behavioral characteristics with controls. Compared with women negative for both HPV 16/18 and HSV-2, those positive for HSV-2 alone had a relative risk of 1.2, those positive for HPV16/18 DNA alone had a relative risk of 4.3 (95% CI = 3.0, 6.0), and those positive for both HSV-2 and HPV16/18 had a relative risk of 8.8 (95% CI = 5.9, 13.0), suggesting a possible biological interaction. Furthermore, HSV-2 was found to be persistent in a few selected cervical cancer tumors.[42] On the other hand, evidence for HSV-2 infection, measured by antibody testing, can be found in only one third to one half of patients with cervical dysplasia or cervical cancer,[43,44] and even less often in cervical cancer biopsy specimens.[45]

Risk Factors -- Cervical Tar Exposures

Tar was the first chemical agent associated with cancer. In 1775, Percival Pott observed that scrotal cancer occurred among chimney sweeps in London and was associated with exposure to coal soot.[46] Since then, numerous tar-related exposures have been associated with a variety of cancers.[47-49]

Tar-based vaginal douching was associated with the development of cervical cancer by several American investigators. In 1931, Smith[50] noted use of *Lysol* douches was significantly more common among cases than among controls. In 1950, Lombard and Potter[51] studied women with cervical cancer in Massachusetts and discovered that "long-continued" douching with coal-tar derivatives was reported by more cases than controls. In 1967, Rotkin[52] 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 *Lysol* vaginal douches. This result led to the voluntary removal of *Lysol* and other tar-based vaginal douche products from the US market.

In 1997, Zhang and colleagues[53] reported the results of a meta-analysis of 6 studies of vaginal douching and cervical cancer. Four studies were conducted in the United States and published in 1979, 1986, 1987, and 1991; 2 in Latin America were published in 1990 and 1995.[54-59] The combined results suggest a weak overall effect (pooled RR = 1.25, 95% CI = 0.99, 1.59). Among women who douched at least once per week, the pooled adjusted relative risk was 1.86 (95% CI = 1.29, 2.68). Of note, these statistically significant differences were for vaginal douching with any product, not limited to tar-based douche products.[53] In fact, none of the 6 studies presented data on tar-based douche products separate from other douche products.[54-59]

Cigarette smoking represents another form of exposure to a tar-based carcinogen and has been linked to cervical cancer.[60,61] In 1977, Winkelstein[62] hypothesized that cigarette smoking was a causative factor for cervical cancer. He found a correlation between the age-adjusted incidence rates for cervical cancer and male lung cancer. He noted the results of 4 case-control studies demonstrating more smoking by women with cancer.[63] We have updated and expanded Winkelstein's review and found support for his conclusions.[19,64] Investigators at Johns Hopkins University have recently published data supporting passive cigarette smoking as a risk factor for cervical cancer.[65]

Tobacco smoke contains and delivers over 4000 compounds - some of which are known carcinogens, such as benzyl (a) pyrenes, polycyclic aromatic compounds, and the tobacco specific nitrosamines. One such compound is NNK or 4-(methylnitrosamino)-1-(3-pyridyl) -1- butanone. The cervical mucus of cigarette-smoking women contains 3 times the levels of NNK compared with the cervical mucus of nonsmokers, presumably delivered to the cervix via the blood.[66]

If smoking is an etiologic factor in cervical cancer causation, it is clearly not a necessary one and appears less important as a risk factor for cervical cancer in the developing world. Steckley and colleagues[19] correlated cigarette smoking prevalence with cervical cancer rates in 44 US states, 30 countries of Europe, and 74 countries worldwide. Although there was a reasonable positive correlation between smoking and cervical cancer in the United States, there was a statistically significant *negative* correlation between smoking prevalence and cervical cancer worldwide. In Africa, where cervical cancer rates were the highest in the world, smoking rates were generally the lowest.[19]

Another tar-based compound associated with cervical cancer and possibly the most important on a global scale is derived from carcinogens generated by burning wood in kitchen stoves or ovens. A case-control study was conducted in Honduras to identify cofactors for invasive cervical cancer. Among HPV-positive women, a dose-response relationship was observed for exposure to wood smoke and cervical cancer that persisted in multivariate analysis.[34] In a follow-up study by the same group of investigators, 125 women with CIN (CIN I, CIN II or CIN III) in Honduras were compared with 241 age- and clinic-matched controls. Chronic exposure to wood smoke significantly increased the risk of CIN III. It is plausible that chronic inhalation of carcinogens derived from wood smoke could have an effect on the progression to cervical cancer, similar to that observed for cigarette smoking.[67]

Discussion

The key to gaining insights into the etiology of cervical cancer and, for that matter, all cancers, is to organize facts and data into coherent, testable, scientific theories.[68] One can propose that squamous cell cervical cancer results from a synergistic interaction among oncogenic sexually transmitted agents, principally HPV-16, HPV-18, and possibly HSV-2, and cervical tar exposures, such as active and passive cigarette smoking, tar-based vaginal douches, and/or inhaling the smoke produced by coal- or wood-burning stoves in poorly ventilated kitchens.

One could test the virus-tar hypothesis by epidemiologic examination of case-controls in diverse populations. Potential determinants of cervical cancer could be sought by employing a 2-factorial model looking for a synergistic interaction between oncogenic sexually transmitted virus(es) and a composite cervical tar exposure measure. Any cervical cancer patient found without any evidence of prior HPV infection should undergo a most thorough clinical and epidemiologic evaluation. Additionally, one could test the hypothesis in animal models. For example, one might re-enact the Rous rabbit models of squamous cell cancers evaluating cytokines, oncogenes, aneuploidy, and other potential molecular measures of carcinogenesis prospectively.

The highest incidence rates of cervical cancer are reported in sub-Saharan Africa and Central America (Table). Incidence rates are generally lower in developed countries and areas, such as the United States, but this appears to represent a decline in cervical cancer incidence over the last century (Figure 2). This decline is generally attributed to successful screening programs using the Papanicolaou test and/or to rising hysterectomy rates. Although we agree that the "Pap test" is a life-saving intervention for many women, we find it difficult to attribute declining incidence of cervical cancer throughout the 20th century to Papanicolau testing, given the fact that George N. Papanicolaou (1883-1962) did not read his paper before the New York Obstetrical-Gynecological Society until 1938 and did not publish his work until 1941, by which time a decline in uterine cancer rates had already been realized in the United States.[69] Even so, Dr. Papanicolaou's studies were not readily accepted by pathologists and clinicians, and his tests of vaginal/cervical smears were not generally implemented in the United States until the 1950s.[70] Perhaps there was also a temporal correlation between changing cooking styles (ie, from wood- and coal-burning to gas and electricity) and the 20th century decline in cervical cancer rates in the United States and elsewhere.

The hypothesis clearly identifies HPV as the main etiologic factor for cervical cancer and supports the importance of developing and implementing HPV vaccines as a primary preventive strategy. Papanicolaou testing augmented with increasing use of HPV-specific testing remains a life-saving intervention for many women. The hypothesis also gives public health officials additional rationale to discourage cigarette smoking among women and to identify and treat sexually transmitted diseases. Linking cervical cancer risk directly to cigarette smoking might reduce tobacco initiation rates and stimulate greater discontinuation rates in young women. Furthermore, the hypothesis might motivate heathcare providers and public health officials to discourage use of and/or remove tar-based vaginal douche products from worldwide markets. This hypothesis also suggests that indoor pollution resulting from the use of wood for cooking/heating is a risk factor for cervical cancer in HPV-infected women. Given both the highest prevalence of cervical cancer and wood-burning in developing countries, this risk factor deserves further study.

A major limitation of this review is an inability to fully address whether HPV infection is a necessary cause of cervical cancer. One cannot ascertain whether there exist HPV-negative cervical cancer patients. Over 100 different HPV genotypes have been sequenced, but there are at least 100 more that still need to be analyzed.[71] How should medical epistemologists interpret findings demonstrating that HPV can be found in roughly 95% of cervical cancer patients but not in the remaining 5%?

The fact remains that large populations around the globe are exposed to both HPV and tars and do not get cervical cancer. This virus-tar hypothesis does not account for several other important factors related to HPV infection. For example, most HPV infections regress spontaneously, suggesting that immunologic factors must contribute to pathogenesis. Our discussion of geography and cervical cancer ignores male and female behavioral factors and does not account for other causes of death with similar behavioral etiologies, such as AIDS.

Cervical cancer remains a serious public health problem worldwide. Therefore, more research on the risk factors for cervical cancer is warranted to better understand its etiology and pathogenesis. Although the etiology of cervical cancer appears to be complex and multifactorial, several risk components can be characterized, and potentially beneficial interventions can be designed, implemented, and evaluated.

Table. Cervical Cancer, Smoking Rates, and Gross Domestic Product per Capita by Country

Country	Cervical Cancer per 100,000 (Rank)	Percent Female Smokers (Rank)	GDP per Capita (Rank)
Zambia	61.08 (1)	10.0 (54)	880 (73)
Swaziland	52.16 (2)	2.1 (69)	4,200 (49)
Zimbabwe	52.09 (3)	1.2 (71)	2,400 (61)
Lesotho	45.75 (4)	1.0 (72)	2,400 (61)
Ecuador	44.18 (5)	18.3 (37)	4,800 (46)
Guatemala	44.00 (6)	17.7 (40)	3,800 (55)
Paraguay	41.10 (7)	5.5 (62)	3,700 (56)
El Salvador	40.56 (8)	12.0 (50)	3,000 (59)

Mexico	40.49 (9)	18.4 (35)	8,300 (35)
Peru	39.95 (10)	15.4 (43)	4,300 (48)
Dominican Republic	38.41 (11)	17.1 (42)	5,000 (44)
Venezuela	38.33 (12)	39.2 (1)	8,500 (34)
Honduras	36.65 (13)	11.0 (52)	2,400 (61)
Samoa	32.86 (14)	24.0 (22)	2,100 (66)
Romania	31.50 (15)	15.2 (45)	4,050 (53)
Brazil	31.26 (16)	29.3 (10)	6,100 (42)
Panama	31.23 (17)	20.0 (31)	7,300 (38)
Chile	29.15 (18)	18.3 (37)	12,500 (28)
South Africa	28.86 (19)	11.0 (52)	6,800 (39)
Bangladesh	27.64 (20)	10.0 (54)	1,380 (70)
Nepal	26.47 (21)	15.4 (44)	1,100 (72)
Mauritius	26.46 (22)	3.3 (67)	10,000 (32)
Costa Rica	24.96 (23)	6.6 (59)	6,700 (41)
Namibia	24.70 (24)	35.0 (2)	4,100 (50)
Cuba	23.85 (25)	26.3 (18)	1,560 (69)
Algeria	23.39 (26)	6.6 (59)	4,600 (47)
Philippines	22.66 (27)	18.0 (39)	3,500 (58)
Bahamas	22.06 (28)	4.0 (65)	20,100 (19)
Hungary	22.05 (29)	27.0 (15)	7,400 (37)
Poland	21.05 (30)	19.0 (32)	6,800 (39)
Bulgaria	20.94 (31)	23.8 (24)	4,100 (50)
Denmark	19.02 (32)	30.0 (6)	23,300 (7)
Slovenia	18.88 (33)	20.3 (30)	10,300 (30)
Mongolia	17.97 (34)	19.0 (32)	2,250 (65)
Albania	17.78 (35)	6.3 (61)	1,490 (71)
Vietnam	17.57 (36)	4.3 (64)	1,770 (68)
Slovakia	16.59 (37)	30.0 (6)	8,300 (35)
Lithuania	16.06 (38)	8.6 (57)	4,900 (45)
Estonia	15.52 (39)	21.7 (29)	5,500 (43)
Czech Republic	15.09 (40)	12.0 (50)	11,300 (29)
Singapore	14.89 (41)	3.1 (68)	26,300 (4)
Portugal	14.60 (42)	7.1 (58)	14,600 (25)
Argentina	14.16 (43)	34.0 (3)	10,300 (30)
Uruguay	13.85 (44)	14.3 (47)	8,600 (33)
Russian Federation	13.58 (45)	14.0 (48)	4,000 (54)
Norway	12.60 (46)	32.3 (4)	24,700 (5)
Austria	11.90 (47)	19.0 (32)	22,700 (9)
Germany	11.53 (48)	30.0 (6)	22,100 (15)
Japan	11.11 (49)	13.4 (49)	23,100 (8)
New Zealand	10.61 (50)	24.0 (22)	17,000 (23)

Iceland	10.41 (51)	28.0 (11)	22,400 (12)
France	10.14 (52)	27.0 (15)	22,600 (11)
Sweden	9.35 (53)	22.3 (27)	19,700 (20)
United Kingdom	9.34 (54)	28.0 (11)	21,200 (16)
Latvia	9.25 (55)	18.4 (35)	4,100 (50)
Belgium	9.09 (56)	26.0 (19)	23,400 (6)
Italy	9.05 (57)	17.3 (41)	20,800 (18)
Uzbekistan	8.31 (58)	1.0 (72)	2,500 (60)
Canada	8.25 (59)	23.0 (26)	22,400 (12)
Ireland	7.87 (60)	31.0 (5)	18,600 (21)
USA	7.84 (61)	22.1 (28)	31,500 (2)
Netherlands	7.28 (62)	30.6 (6)	22,200 (14)
Switzerland	7.23 (63)	27.4 (14)	26,400 (3)
Spain	7.20 (64)	24.7 (21)	16,500 (24)
Australia	7.14 (65)	23.2 (25)	21,200 (16)
Greece	6.92 (66)	28.0 (11)	13,400 (26)
Pakistan	6.47 (67)	9.0 (56)	2,000 (67)
Kuwait	5.78 (68)	1.9 (70)	22,700 (9)
Israel	5.76 (69)	25.0 (20)	18,100 (22)
Malta	5.65 (70)	14.6 (46)	13,000 (27)
China	5.24 (71)	3.8 (66)	3,600 (57)
Luxembourg	3.58 (72)	27.0 (15)	32, 700 (1)
Iraq	3.27 (73)	5.0 (63)	2,400 (61)

Modified from Steckley et al, 2003.[19]

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