Herpes simplex virus type 2 and cancer: A medical geography approach

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Herpes simplex virus type-2 (HSV-2) has been identified as a possible aetiological agent of cancer in humans, especially prostate cancer, but results remain controversial. Here, we have addressed this question using a medical geography approach based on the national incidence of various cancers and seroprevalence of HSV-2 in 64 countries worldwide. We corrected reports of cancer incidence for national gross domestic product (GDP) because living in a wealthy nation likely increases the probability of having a cancer detected. Data were also corrected for latitude and diet. Our analysis not only confirms that prostate cancer and HSV-2 seroprevalence are positively associated, but it also reveals the existence of a positive relationship between HSV-2 and melanoma incidence in both men and women. These results, though correlational, suggest that HSV-2 should continue to be investigated as a possible oncogenic pathogen of humans.

1. Introduction

Since the mid-1970s, it has been increasingly recognized that infectious agents can cause cancers (see De Martel and Franceschi, 2009 for a recent review). For instance, worldwide incidences of cancers of the liver, stomach, and cervix uteri are largely attributable to hepatitis B and C viruses, to the bacteria *Helicobacter pylori*, and to human papilloma virus, respectively. However, the complete list of oncogenic pathogens is far from being definitively established (e.g., Cochran et al., 2000; Ewald, 2009). Identifying infectious agents that directly or indirectly contribute to oncogenesis remains a priority in the war on cancer for an obvious reason: since infectious diseases are often preventable or treatable, cancers associated with these infections could potentially be preventable as well (De Martel and Franceschi, 2009).

Herpes viruses (approximately 100 members, with eight found to infect humans) possess numerous attributes of oncogenic viruses (Ewald, 2009): they persist in the host by establishing a latent infection, they are mutagenic and inhibit apoptosis, and they stimulate host DNA synthesis. Such alterations can result in the derailment of the normal cell cycle and ultimately cause cancer. Not surprisingly, herpes viruses have been implicated as aetiological factors in several human malignancies (Shillitoe and Silverman, 1979; Eglin et al., 1983; Young and Rickinson, 2004; Parker et al., 2006; Horikawa et al., 2007; Filippakis et al., 2010; Mesri et al., 2010; Petrova and Kamburov, 2010). Among them, herpes simplex virus type 2 (HSV-2), which is the most common cause of recurrent genital ulcers in the world, has been linked to prostate cancer (Boldogh et al., 1983; Haid and Sharon, 1984; Dennis et al., 2009) and to invasive cervical cancer when occurring in conjunction with human papillomavirus (Smith et al., 2002). However, the exact role of HSV-2 in causing or promoting cancers remains controversial because HSV-2 is not systematically detected in tumours (see for instance Herbert et al., 1976; Baker et al., 1981; Serfling et al., 1992; Taylor et al., 2005; Sutcliffe, 2010). In addition, it is difficult to determine whether HSV-2 is a true causal factor or whether it is correlated to other oncogenic sexually transmitted infections. Finally, it has also been demonstrated that cells may acquire increased susceptibility to HSV-2 during tumour progression (Jensen et al., 2010).

Here, we explore the links between infection by HSV-2 and a large variety of cancers in humans using a medical geography approach. We conducted a comparative study using data from populations throughout the world since marked variations exist between countries in both the incidence of cancers and the seroprevalence of HSV-2.

2. Material and methods

2.1. Data sources

International statistics on 46 cancers in men and women (lip oral cavity; nasopharynx; other pharynx; oesophagus; stomach;

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colorectum; liver; gallbladder; pancreas; larynx; lung; melanoma of skin; breast; cervix uteri; corpus uteri; ovary; kidney; bladder; brain, nervous system; thyroid; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; leukaemia; prostate; testis) were obtained from the International Agency for Research on Cancer (IARC GLOBOCAN project, 2008, http://globocan.iarc.fr/). We did not include mortality data in our analysis since this variable is influenced by the access to therapies—a parameter that strongly varies between countries. Instead, we used incidence data (age-standardised rate) that derive from population-based cancer registries. While data from most of the developing countries might not be of the highest quality, this information is still of unique importance as it often remains the only relatively unbiased source of information available on the profile of cancer (see http://globocan.iarc.fr/). Data on dietary energy consumption, in kcal/person/day, were from FAO (http://www.fao.org/economic/ess/food-security-statistics/en/).

Table 1
HSV-2 prevalence estimates from non-high-risk population by country.

Country	Seroprevalence of HSV-2	Mean or median age	Reference
Australia	14	32	Smith and Robinson (2002)
Bangladesh	15.4	27.9	Bogaerts et al. (2001)
Barbados	34.2	35	Levett (2005)
Belgium	11.1	32	Pebody et al. (2004)
Benin	26.5	32	Smith and Robinson (2002)
Brazil	34.4	36	Cowan et al. (2003)
Bulgaria	23.9	32	Pebody et al. (2004)
Burkina Faso	17.9	24	Kirakoya-Samadoulougou et al. (2008)
Cameroon	55	32	Smith and Robinson (2002)
Canada	19	32	Smith and Robinson (2002)
Central African Republic	82	27	Smith and Robinson (2002)
China	29	52	Smith and Robinson (2002)
Colombia	56.9	47	Patnaik et al. (2007)
Costa Rica	39	34.5	Smith and Robinson (2002)
Croatia	8.7	39	Rode et al. (2008)
Czech republic	6	27	Pebody et al. (2004)
Denmark	40	32	Smith and Robinson (2002)
Erythrea	23	28	Smith and Robinson (2002)
Estonia	15.9	30.5	Cowan et al. (2003)
Ethiopia	35.1	26.5	Mihret et al. (2002)
Finland	16	33	Malkin (2004)
France	15.7	37.5	Malkin (2004)
Gabon	66	37	Ozouaki et al. (2006)
Gambia	32.5	32	Smith and Robinson (2002)
Germany	13.9	32	Pebody et al. (2004)
Groënland (Denm)	74	32	Smith and Robinson (2002)
Haiti	54	25	Smith and Robinson (2002)
Hungary	4	34.5	Hettmann et al. (2008)
India	12.4	31.1	Cowan et al. (2003)
Indonesia	18.6	31	Davies et al. (2007)
Israël	6.4	40.5	Smith and Robinson (2002)
Italia	4.8	30	Malkin, 2004
Japan	1	38	Malkin (2004)
Kénya	71	32	Smith and Robinson (2002)
Malawi	64.3	29.5	Sutcliffe et al. (2002)
Mali	43.3	45	Patnaik et al. (2007)
Mexico	24	44.5	Smith and Robinson (2002)
Morocco	26	40	Patnaik et al. (2007)
Netherlands	8.8	27	Pebody et al. (2004)
New Zealand	11.5	26	Smith and Robinson (2002)
Norway	34	35	Malkin (2004)
Papoua New Guinea	27.4	32	Suligoi et al. (2005)
Peru	35,7	48	Patnaik et al. (2007)
Philippines	9.2	47	Smith and Robinson (2002)
Poland	9.15	34	Smith et al. (2002)
Porto Rico (US)	15.5	34.5	Pérez et al. (2010)
Russia	20.3	46.4	Khryanin and Reshetnikov (2007)
Senegal	22	25.2	Diawara et al. (2008)
South Africa	66.5	23	Smith and Robinson (2002)
Spain	9.4	52	Patnaik et al. (2007)
Sri Lanka	17.65	37.6	Cowan et al. (2003)
Sweden	35	33	Malkin (2004)
Switzerland	11.3	34.5	Malkin (2004)
Syria	0	25.5	Smith and Robinson (2002)
Tanzania	57	29.5	Smith and Robinson (2002)
Thaïland	34.6	51	Patnaik et al. (2007)
Turkey	37	35.5	Smith and Robinson (2002)
Uganda	82	34.5	Smith and Robinson (2002)
England	4.2	37	Pebody et al. (2004)
USA	28	34.5	Malkin (2004)
Vanuatu	30	25.8	Haddow et al. (2007)
Vietnam	21.9	39.5	Le et al. (2009)
Zambia	63.5	32	Smith and Robinson (2002)
Zimbabwe	33	33	Smith and Robinson (2002)

International statistics on HSV-2 infection prevalence were obtained from the few review papers available on this topic (Smith and Robinson, 2002; Malkin, 2004; Pebody et al., 2004; Patnaik et al., 2007) and completed by an extensive search of the literature mainly using ISI Web of Knowledge and PubMed. Search keywords included HSV-2, genital herpes prevalence, seroprevalence, epidemiology, and seroepidemiology. The only data used were from peer-reviewed articles that provided a clear description of the type-specific serologic methodology for detection of HSV-2 antibodies as well as the age (median or mean) of the participants (except for Barbados, for which the age information was obtained by contacting the author). We considered data only on non-high risk populations. When herpes data were available for both males and females, we calculated the mean value.

2.2. Analyses

The influence of HSV-2 prevalence on the incidence of several cancers was examined using linear regression; data on cancer incidence were log-transformed for the analysis. Since herpes prevalence often increases with age (e.g., Smith and Robinson, 2002), we included the mean or median age of the populations used to estimate HSV-2 prevalence in the models. In addition, cancer detection might vary among nations: living in a wealthy country probably increases the likelihood of cancer detection. We controlled for national wealth by including the logarithm of per capita GDP (gross domestic product) in the models. Two other potentially confounding variables were included: the average daily caloric intake and the absolute value of latitude as a means to summarize environmental factors. Male and female cancers were analyzed independently, standard Bonferroni corrections being applied separately for the 22 male cancers and the 24 female cancers.

3. Results

Data on the seroprevalence of HSV-2 were obtained for 64 countries (Table 1).

The results of the linear regression models for the three cancers associated with HSV-2 prevalence—prostate cancer and melanoma in both men and women are summarized in Table 2, where odds-ratios are given for a 10% increase in HSV-2 prevalence. Prostate cancer was significantly associated with HSV-2 after Bonferroni correction, whereas the association between male and female melanoma and HSV-2 prevalence was only marginally significant.

Table 2
Association of HSV-2 prevalence and cancer incidences. Odds-ratios and 95% confidence intervals are given for a 10% increase in HSV-2 prevalence.

Cancer	Odds-ratio (95% C.I.)	*P*-value	Bonferroni-corrected significance threshold
Prostate	1.26 (1.12–1.41)	0.00024	0.0022
Melanoma (male)	1.25 (1.09–1.44)	0.0026	0.0022
Melanoma (female)	1.27 (1.09–1.49)	0.0031	0.0021

Among the confounding variables, per capita GDP and caloric intake were positively associated with those cancer incidences, as expected

4. Discussion

Despite considerable research, the causes of most cancers remain a mystery. Because our approach is correlative, it is not possible to prove causation or to exclude the possibility of spurious results (i.e., a non-causal correlation between cancer and ecological variables that influence HSV-2 transmission). Despite these limitations, the present work suggests that HSV-2 should continue to be investigated as a possible oncogenic pathogen of humans.

HSV-2 seroprevalence was significantly associated with the incidence of prostate cancer. The existence of a positive association between HSV-2 and prostate cancer is consistent with previously published studies (e.g., Herbert et al., 1976; Boldogh et al., 1983; Haid and Sharon, 1984; Dennis et al., 2009), but to our knowledge this is the first time that such an association is detected at this geographical scale. Our results could also support the hypothesis that prostate cancer is associated to sexually transmitted diseases in general, not necessarily HSV-2, and/or that HSV-2 could just act as a cofactor (Korodi et al., 2005; Huang et al., 2008). In addition, we cannot totally exclude a surveillance bias: for instance, if men with HSV-2 are followed more closely than uninfected men and are therefore screened for prostate cancer more accurately, we would expect a positive association between HSV-2 and prostate cancer even if no causal link exists. Nevertheless, if a causal relationship exists, it can only be in the direction of STIs to prostate cancer.

The statistical association between HSV-2 and melanoma in both men and women, although only marginally significant, deserves to be considered, since first, the Bonferroni correction is known to be overly conservative, and second, it is unlikely that the male and female incidences of a same disease were picked up by hazard, especially since latitude was controlled for. This association is intriguing and invites further exploration before we can consider this virus as a possible causative agent for melanoma genesis. At present, very few studies have linked herpes viruses and human melanoma. However, metastatic spread of melanomas mimicking herpes zoster has been reported in three studies (North et al., 1998; Evans et al., 2003; Zalaudek et al., 2003). Here, it is relevant to first note that the association is detected despite the fact that melanomas are usually more common in people with lightly pigmented skin while HSV-2 seroprevalence is highest in southern countries. Lundberg et al. (2006) pointed out that melanomas can also emerge on sun-sheltered body surfaces, i.e., nasal cavity, anus, rectum, vulva, and penis. However, none of the eight herpes viruses infecting human seems to play a major role in the development of these extracutaneous melanomas (Lundberg et al., 2006). In addition, extracutaneous melanomas are few in absolute numbers compared with cutaneous ones. Skin cancer has been linked to herpes viruses, but it concerns non-melanoma skin cancer and cytomegalovirus (Zafiropoulos et al., 2003). Thus, the positive link between HSV-2 seroprevalence and the incidence of melanoma detected here remains enigmatic.

Further research is necessary to determine the potential mechanism(s) for HSV-2 initiating or promoting prostate cancer and melanomas. Similarly, given the high number of people who are infected with HSV-2 worldwide compared with those who have cancers, it appears clear that this virus alone does not cause cancer. Determining the other underlying causes of cancer initiation in people infected with HSV-2 is therefore essential. In addition, because HSV-2 transmission is potentially correlated to that of other sexually transmitted pathogens, our study draws attention to the need to assess whether other sexually transmitted pathogens are responsible for prostate cancer and melanoma.

We would like to underline some potential limitations of our study. Sources of environmental heterogeneity at the largest spatial scale are extraordinarily various and undoubtedly cannot be all considered in our analysis when attempting to understand variation in cancer incidence. As frequently argued, comparative analyses at the largest scale have to be interpreted with caution because data are collected using different methods or they come from different sources. Although this argument holds true when no significant result is detected (i.e., data are not strong enough to detect a potentially significant result), it is usually unlikely to be relevant when significant trends are found, since a biological trend has a priori no reason to be correlated to background noise in the data set (Brown, 1995; Lawton, 1999). However, we must be aware that despite our efforts to control for such effects, we cannot exclude the possibility that other parameters, at a different scale, may confound our conclusions.

Conflict of interest statement

We declare no conflict of interest.

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