A Population Based HPV Immunization Program in British Columbia: *Background Paper*

January 17, 2006

Cancer Prevention Program

BC Cancer Agency

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Acknowledgments

Research and writing support for this project has been provided by:

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Background Paper

Executive Summary

The fact that viral infections can cause cancer has been suspected for over a hundred years, beginning with the observed association between cervical cancer and having multiple sexual partners. Intense research has recently identified that 90% or more of cervical cancers can be traced to human papillomavirus (HPV) types 16 and 18, plus another dozen probable types. This conclusion is unique in cancer research; no other cancer in humans has been shown to have such a clear and necessary cause. In turn, this discovery has afforded an unprecedented opportunity for cancer control.

In addition to cervical cancers, HPV infection has been implicated in a number of anogenital and head and neck cancers. Current research suggests an even broader involvement of HPV infections in carcinogenesis, including non-melanoma skin cancers, lung cancers, and bladder cancers. Given the extensive range of cancers and sites in which HPV has been detected, it might be a fairer question to ask what the virus is *not* involved with, especially in reference to the epithelial and mucosal tissues for which it seems to have a great affinity.

And cancer is not the whole story. Certain HPV types, while showing low oncogenic risk, have been connected to non-malignant diseases, including genital warts, recurrent respiratory papillomatosis (RRP), sinonasal papillomas and conjunctival papillomas.

A Vaccine Targeting HPV

There has been a great deal of excitement and energy around creating and testing a vaccine targeting HPV. Many challenges exist in the development of such a vaccine. Because of the multiplicity of HPV types which are oncogenic, there is motivation to make any vaccine polyvalent, but this adds development and manufacturing expense. Thus the “balancing act” in terms of resource investment involves targeting those viral types (out of the approximately 200 different HPV types have been identified to date) that cause the greatest proportion of cancers and non-malignant disease

There have been a number of published studies exploring either preventive or therapeutic HPV vaccines in humans, while other research is still in progress. Based on the results of the studies to date, it appears that a vaccine for HPV is both highly efficacious and very well-tolerated. Efficacy ranges from 90 to 100%. The lower

efficacy seems to be seen when vaccination protocols are not completely followed or when vaccines target multiple HPV types in a less select group of women (e.g., including those with a previous HPV infection).

As the potential launch date for an HPV vaccine nears, however, questions remain regarding the applicability of such a vaccine in nations with comprehensive cervical screening programs. Indeed, this is the key issue which prompted this background paper.

Is An HPV Vaccination Program Cost-effective?

A number of research groups have addressed the issue of the cost-effectiveness of a vaccination program using mathematical modeling of disease progression and the impact of a vaccine. How would a program perform over the long-term, especially compared to current screening strategies?

The mathematical modeling of disease progression and the impact of a vaccine is complex, requiring a host of assumptions reflecting incomplete knowledge. Despite these limitations, cost-effectiveness analysis and disease-simulation models provide valuable information in the absence of real-world experience.

While the modelling research completed to date has a number of significant limitations, there are several consistent themes that appear. First, an HPV vaccination program would have an impact similar to that of a number of other routinely accepted vaccination programs. Second, a vaccination program targeting 12-year-old girls appears to be the most cost-effective approach. Including boys in a vaccination program improves effectiveness, but only modestly and at a high cost. Third, an HPV vaccination program will not eliminate the need for screening programs but may allow for later initiation and less frequent testing. And fourth, implementing a combined vaccination and screening program that would reduce the life-time mortality from cervical cancer by approximately 90% would cost in the neighbourhood of $45,000 to $60,000 (2002 US dollars) per QALY gained.

Key components of this background paper comprise estimating the clinical and medical-cost impact of HPV infection in British Columbia, estimating the potential clinical and medical-cost impact of implementing an HPV vaccination program in the province, and placing this information in the context of the potential costs associated with implementing a vaccination program.

The Clinical Burden of HPV Infection in British Columbia

In determining the clinical burden of HPV infection in British Columbia, we began with current B.C. Cancer Agency data on both the actual number of new cervical cancer cases in the province and projections to the year 2018. For the relevant anogenital cancers (vagina, vulva, anus, penis) and the relevant head and neck cancers (larynx, oral cavity, nasal cavity, tonsil, conjunctiva), we accessed information on the number of new cases over the five-year period from January 1, 1999 to December 31, 2003. The average five-year rate was then applied to B.C. population projections to estimate the annual number of new cases in the province in the future.

We identified that there were 151 new cases of cervical cancer, 159 new cases of anogenital cancers with potential HPV implication, and 173 new cases of head and neck cancers with potential HPV implication in the calendar year 2003.

While there is virtually a 100% correlation between cervical cancers and HPV infection, this is not the case for most of the other cancers. Based on the best currently available data, HPV infection is directly involved in the following proportion of cancers:

Cancer	HPV Involvement
Cervix	100%
Anus	88%
Vulva	55%
Vagina	54%
Tonsil	51%
Conjunctiva	50%
Penis	42%
Larynx	25%
Oral	22%
Nasal	22%

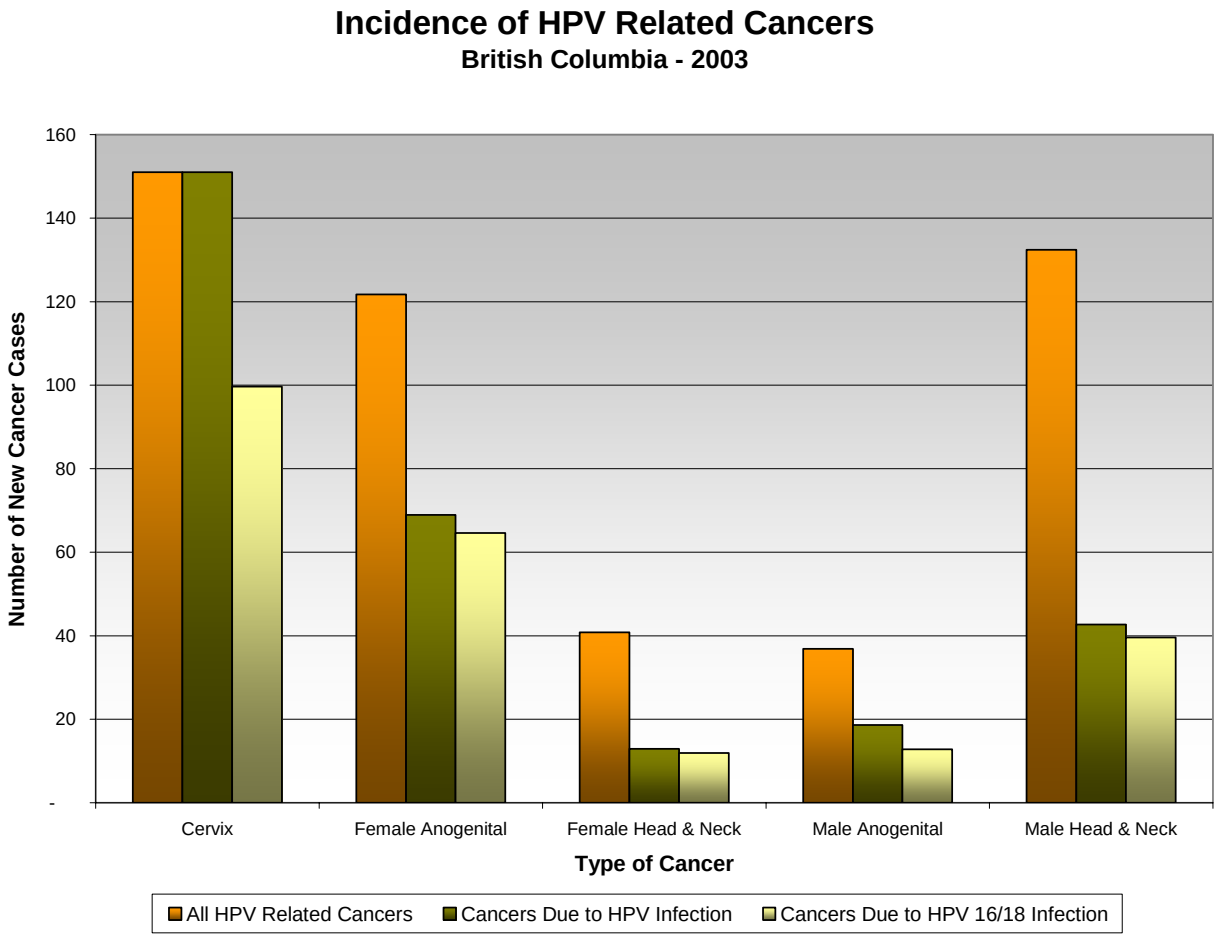
These proportions were applied to the previous figures and used to calculate the number of cervical (151), anogenital (87) and head and neck cancers (56) in B.C. attributable to HPV infection. Thus, while there were an estimated 483 new HPV-related cervical, anogenital and head and neck cancers in 2003 in B.C., only 294 (61%) of these cancers are directly associated with HPV infection.

HPV 16 and 18 are the most common types associated with cancers, but they are clearly not the only types implicated. It is useful to calculate the proportion of the 294 new cancers in 2003 that were associated with HPV 16/18 infection. Based on the best available data, HPV 16/18 infection is involved in the following proportion of each type of cancer with direct HPV involvement:

Cancer	HPV 16/18 Involvement
Cervix	66%
Anus	80%
Vulva	100%
Vagina	71%
Tonsil	84%
Conjunctiva	100%
Penis	63%
Larynx	100%
Oral	100%
Nasal	100%

These proportions were used to calculate the number of cervical, anogenital and head and neck cancers in B.C. due to HPV 16/18 infection. Of the 294 cancers directly associated with HPV infection in 2003, 229 (78%) are associated with HPV 16/18. The remainder of the new cases (a total of 65) are associated with a variety of other HPV types.

As a "snapshot" of one particular year, information on the number of new cancer cases in B.C. in 2003 that were potentially related to HPV infection, the subset actually attributable to HPV infection, and those associated with HPV 16/18 infection in particular are summarized on the following chart.



To estimate the annual number of cases of genital warts, recurrent respiratory papillomatosis, and sinonasal papilloma, we applied incidence rates found in the literature to the B.C. population. We were unable to find appropriate information on incidence rates for conjunctival papilloma.

Based on the best available data, we estimated that there were 6,985 new cases of genital warts, 6 cases of recurrent respiratory papillomatosis in children and 59 in adults, and 25 new cases of sinonasal papilloma in 2003 due to HPV infection.

The vast majority of these non-malignant diseases are associated with HPV types 6 and/or 11. In fact, an estimated 90% of genital warts, 76% of recurrent respiratory

papillomatosis and 33% of sinonasal papilloma cases are associated with HPV 6/11 infection. Using this information, we estimated that there were 6,286 new cases of genital warts, 5 cases of recurrent respiratory papillomatosis in children and 45 in adults, and 8 new cases of sinonasal papilloma in 2003 due to HPV 6/11 infection.

As noted earlier, similar incidence data for 2004, 2005, and subsequent years were also estimated for both cancers and non-malignant disease. The 2005 projection in particular will be used in the financial analysis which follows.

The Financial Burden of HPV Infection in British Columbia

A considerable amount of financial information is available in the literature with respect to treating HPV-related cervical disease, including the costs of routine cervical screening, the detection and management of cervical precancers, and the treatment of cervical cancers. Much less information is available, however, for other malignant and non-malignant diseases associated with HPV.

We have used the available costing information to generate the results summarized on the following table.

Estimated Cost of Treating
HPV related Diseases in BC in 2005

	Cost / Case Procedure
Cervical Cancer	
Conventional Cytology	$ 40
Colposcopy	$ 139
Precancers	$ 984
Local Invasive Cervical Cancer	$ 11,716
Regional Invasive Cervical Cancer	$ 23,749
Distant Invasive Cervical Cancer	$ 35,979
Anogenital Cancers	
Vulva	$ 31,139
Vagina	$ 37,787
Penis	$ 37,787
Anus	$ 44,434
Cancers of the Head and Neck	
Tonsils	$ 26,103
Larynx	$ 47,912
Sinonasal	$ 63,599
Oral	$ 63,418
Non-Malignant Diseases	
Genital Warts	$ 549
Recurrent Respiratory Papillomatosis	
Children	$ 143,827
Adults	$ 100,679

Whenever possible, we have used costs from multiple sources and countries. We have also used data which take into account a fuller costing than just the direct one-time treatment costs of the cancers. For example, cancer treatment costs include assessment, treatment, recurrence and longer term follow-up costs. As a further case, the costs for RRP in children take into account the fact that the average child with RRP will require 4 operations per year over a 4.2 year time period.

We combined this costing of HPV-related disease treatment with the estimated incidence data in order to estimate the total direct costs of HPV infections in B.C. for

2005. The results are provided on the following tables; first for all types of HPV, and then limited to types 16/18 and 6/11.

In 2005, we estimate the direct cost of HPV-related disease in B.C. to be $50.1 million annually (see following table).

Estimated Cost of HPV Infection in British Columbia in 2005 By Gender

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	577,718	$ 40	$ 23,118,039		**$ 23,118,039**
False Positives			$ 3,250,000		**$ 3,250,000**
Cervical Precancers			$ 6,100,000		**$ 6,100,000**
Local Invasive Cervical Cancer	49	$ 11,716	$ 574,096		**$ 574,096**
Regional Invasive Cervical Cancer	49	$ 23,749	$ 1,163,699		**$ 1,163,699**
Distant Invasive Cervical Cancer	49	$ 35,979	$ 1,762,949		**$ 1,762,949**
Anogenital Cancers					
Vulva	54	$ 31,139	$ 1,681,528		**$ 1,681,528**
Vagina	12	$ 37,787	$ 453,443		**$ 453,443**
Penis	13	$ 37,787		$ 491,230	**$ 491,230**
Anus	12	$ 44,434	$ 266,607	$ 266,607	**$ 533,213**
Cancers of the Head and Neck					
Tonsils	26	$ 26,103	$ 156,099	$ 522,591	**$ 678,689**
Larynx	24	$ 47,912	$ 183,983	$ 965,908	**$ 1,149,891**
Sinonasal	5	$ 63,599	$ 190,796	$ 127,197	**$ 317,993**
Oral	2	$ 63,418	$ 63,418	$ 63,418	**$ 126,837**
Non-Malignant Diseases					
Genital Warts	6,286	$ 549	$ 1,724,154	$ 1,724,154	**$ 3,448,308**
Recurrent Respiratory Papillomatosis					
Children	5	$ 143,827	$ 359,566	$ 359,566	**$ 719,133**
Adults	45	$ 100,679	$ 2,265,268	$ 2,265,268	**$ 4,530,536**
Total			**$ 43,313,644**	**$ 6,785,940**	**$ 50,099,584**

Most of these costs are associated with the female population ($43.3 million or 86%), particularly in regard to the cervical screening program. Costs in the male population are estimated at $6.8 million.

The following tables show the specific costs in 2005 when the disease burden is limited to the four key HPV types which are the possible focus of a vaccination program.

The annual costs associated with HPV 16/18 infection amount to $28.6 million (or 57% of the $50.1 million total).

Estimated Cost of HPV Infection in British Columbia in 2005 for HPV 16/18

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	381,294	$ 40	$ 15,257,905		**$ 15,257,905**
False Positives			$ 2,145,000		**$ 2,145,000**
Cervical Precancers			$ 4,026,000		**$ 4,026,000**
Local Invasive Cervical Cancer	32	$ 11,716	$ 378,903		**$ 378,903**
Regional Invasive Cervical Cancer	32	$ 23,749	$ 768,042		**$ 768,042**
Distant Invasive Cervical Cancer	32	$ 35,979	$ 1,163,546		**$ 1,163,546**
Anogenital Cancers					
Vulva	54	$ 31,139	$ 1,681,528		**$ 1,681,528**
Vagina	9	$ 37,787	$ 321,945		**$ 321,945**
Penis	8	$ 37,787		$ 309,966	**$ 309,966**
Anus	10	$ 44,434	$ 213,285	$ 213,285	**$ 426,571**
Cancers of the Head and Neck					
Tonsils	22	$ 26,103	$ 131,123	$ 438,976	**$ 570,099**
Larynx	24	$ 47,912	$ 183,983	$ 965,908	**$ 1,149,891**
Sinonasal	5	$ 63,599	$ 190,796	$ 127,197	**$ 317,993**
Oral	2	$ 63,418	$ 63,418	$ 63,418	**$ 126,837**
Non-Malignant Diseases					
Genital Warts	-	$ 549	$ -	$ -	**$ -**
Recurrent Respiratory Papillomatosis					
Children	-	$ 143,827	$ -	$ -	**$ -**
Adults	-	$ 100,679	$ -	$ -	**$ -**
Total			**$ 26,525,474**	**$ 2,118,752**	**$ 28,644,225**

The annual costs associated with HPV 6/11 infection amount to $8.8 million (or 18% of the $50.1 million total).

Estimated Cost of HPV Infection in British Columbia in 2005 for HPV 6/11

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	-	$ 40	$ -		**$ -**
False Positives			$ -		**$ -**
Cervical Precancers			$ -		**$ -**
Local Invasive Cervical Cancer	-	$ 11,716	$ -		**$ -**
Regional Invasive Cervical Cancer	-	$ 23,749	$ -		**$ -**
Distant Invasive Cervical Cancer	-	$ 35,979	$ -		**$ -**
Anogenital Cancers					
Vulva	-	$ 31,139	$ -		**$ -**
Vagina	1	$ 37,787	$ 37,636		**$ 37,636**
Penis	1	$ 37,787		$ 40,772	**$ 40,772**
Anus	-	$ 44,434	$ -	$ -	**$ -**
Cancers of the Head and Neck					
Tonsils	1	$ 26,103	$ 4,683	$ 15,678	**$ 20,361**
Larynx	-	$ 47,912	$ -	$ -	**$ -**
Sinonasal	-	$ 63,599	$ -	$ -	**$ -**
Oral	-	$ 63,418	$ -	$ -	**$ -**
Non-Malignant Diseases					
Genital Warts	6,286	$ 549	$ 1,724,154	$ 1,724,154	**$ 3,448,308**
Recurrent Respiratory Papillomatosis					
Children	5	$ 143,827	$ 359,566	$ 359,566	**$ 719,133**
Adults	45	$ 100,679	$ 2,265,268	$ 2,265,268	**$ 4,530,536**
Total			**$ 4,391,307**	**$ 4,405,438**	**$ 8,796,746**

Adding the totals in the two tables, we find that the direct costs related to HPV 16/18/6/11 are about $37.4 million, or 75% of the total when all HPV types are considered. Consistent with epidemiological data presented earlier, the impact of HPV 6/11 is primarily seen in the non-malignant diseases, with only a modest showing in a few cancers.

Implementing an HPV Vaccination Program in British Columbia

With respect to a potential HPV vaccination program in B.C., we made the following assumptions:

- The vaccine will target HPV 16/18/6/11.
- It will be administered to male and female 12 year olds in a three-vaccination protocol at a total cost of $300.
- 80% of male and female 12 year olds will receive the vaccination.
- The vaccine will be 100% efficacious.
- A booster shot will be required at 10 years, with no waning of efficacy during the interim. The booster shot will cost $100.
- The model will run from 2006 to 2031 (i.e., the next 26 years).

Potential Cases Avoided

A key outcome that needs to be tracked is the projected number of cases that will be avoided if the vaccine program is implemented according to the various assumptions delineated. The following two tables identify this data for females and males; the figures basically represent the subset of disease which would have been generated by the targeted viral infections, but which now is eliminated through the effect of the vaccine. For example, the absence of HPV 16/18/6/11 in 80% of 12 year olds will avoid about 2 cervical cancer cases in the tenth year of the program. The number of avoided cases in B.C. will grow to over 16 per year by 2031; this increase represents the latency effect, that is, where disease tends to develop only after persistent infection for years or even decades.

Potential Cases Avoided in British Columbia
Females Vaccinated against HPV 16/18/6/11

Year	Mild Atypia	Moderate or Higher Atypia	Malignant Diseases: Cervix	Vulva	Vagina	Anus	Tonsil	Nasal	Larynx	Non-Malignant Diseases: Genital Warts	RRP
1	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	8	0.11
3	-	-	-	-	-	-	-	-	-	15	0.22
4	-	-	-	-	-	-	-	-	-	66	0.33
5	-	-	-	-	-	-	-	-	-	116	0.44
6	-	-	-	-	-	-	-	-	-	167	0.54
7	-	-	-	-	-	-	-	-	-	215	0.64
8	-	-	-	-	-	-	-	-	-	263	0.90
9	291	109	0.62	0.43	0.04	0.01	0.01	0.04	0.01	369	1.16
10	582	218	1.23	0.85	0.07	0.02	0.02	0.08	0.03	474	1.42
11	872	327	1.85	1.28	0.11	0.03	0.03	0.12	0.04	579	1.67
12	1,152	432	2.44	1.69	0.15	0.04	0.03	0.16	0.05	682	1.92
13	1,426	534	3.02	2.09	0.18	0.05	0.04	0.20	0.06	783	2.17
14	1,696	636	3.59	2.49	0.22	0.06	0.05	0.23	0.08	845	2.42
15	1,964	736	4.16	2.88	0.25	0.07	0.06	0.27	0.09	906	2.67
16	2,226	834	4.71	3.26	0.28	0.08	0.07	0.31	0.10	967	2.92
17	2,490	933	5.27	3.65	0.32	0.09	0.08	0.34	0.11	1,030	3.17
18	2,753	1,032	5.83	4.04	0.35	0.10	0.08	0.38	0.13	1,094	3.42
19	2,965	1,087	7.17	4.43	0.38	0.11	0.09	0.41	0.14	1,138	3.68
20	3,179	1,144	8.52	4.82	0.42	0.12	0.10	0.45	0.15	1,183	3.94
21	3,395	1,201	9.88	5.22	0.45	0.13	0.11	0.49	0.16	1,229	4.20
22	3,617	1,261	11.21	5.62	0.49	0.14	0.12	0.53	0.17	1,278	4.46
23	3,843	1,323	12.53	6.03	0.52	0.15	0.12	0.56	0.19	1,328	4.73
24	4,072	1,387	13.85	6.44	0.56	0.16	0.13	0.60	0.20	1,368	5.00
25	4,306	1,453	15.17	6.86	0.59	0.17	0.14	0.64	0.21	1,409	5.28
26	4,545	1,521	16.48	7.28	0.63	0.18	0.15	0.68	0.23	1,451	5.55

Potential Cases Avoided in British Columbia
Males Vaccinated against HPV 16/18/6/11

Year	Malignant Diseases: Penis	Anus	Tonsil	Nasal	Larynx	Non-Malignant Diseases: Genital Warts	RRP
1	-	-	-	-	-	-	-
2	-	-	-	-	-	8	0.12
3	-	-	-	-	-	15	0.24
4	-	-	-	-	-	28	0.35
5	-	-	-	-	-	40	0.47
6	-	-	-	-	-	51	0.57
7	-	-	-	-	-	63	0.68
8	-	-	-	-	-	74	0.96
9	0.07	0.03	0.02	0.02	0.02	128	1.24
10	0.14	0.06	0.04	0.04	0.05	182	1.51
11	0.21	0.08	0.06	0.06	0.07	236	1.78
12	0.28	0.11	0.07	0.08	0.09	288	2.04
13	0.34	0.14	0.09	0.10	0.11	339	2.31
14	0.41	0.16	0.11	0.12	0.13	429	2.57
15	0.47	0.19	0.13	0.14	0.16	520	2.83
16	0.54	0.21	0.14	0.16	0.18	609	3.10
17	0.60	0.24	0.16	0.18	0.20	697	3.36
18	0.66	0.27	0.18	0.20	0.22	784	3.63
19	0.73	0.29	0.19	0.22	0.24	850	3.90
20	0.79	0.32	0.21	0.24	0.26	916	4.17
21	0.86	0.34	0.23	0.26	0.28	982	4.45
22	0.92	0.37	0.24	0.28	0.30	1,050	4.73
23	0.99	0.40	0.26	0.30	0.33	1,119	5.02
24	1.06	0.42	0.28	0.32	0.35	1,164	5.30
25	1.13	0.45	0.30	0.34	0.37	1,209	5.59
26	1.19	0.48	0.32	0.36	0.39	1,256	5.88

Estimated Cost of an HPV Vaccination Program in British Columbia

For this study, we have followed the lead established by other models and used a base estimate of $300 per vaccination protocol, with a booster shot required at 10 years at a cost of $100. These costs will be varied in a subsequent sensitivity analysis. As noted earlier, an additional assumption is that 80% of male and female 12 year olds will receive the vaccination. These factors enable us to generate the following table, which is dependent on B.C. population projections until 2031.

Estimating the Cost of a Vaccination Program
In Constant 2005 Canadian Dollars

	12 Year Old		Uptake (80%)		Costs - Females			Costs - Males		
Year	F	M	F	M	Original	Booster	**Total**	Original	Booster	**Total**
1	24,574	26,125	19,659	20,900	$ 5,897,760		**$ 5,897,760**	$ 6,270,000		**$ 6,270,000**
2	24,583	26,355	19,666	21,084	$ 5,899,920		**$ 5,899,920**	$ 6,325,200		**$ 6,325,200**
3	24,521	25,935	19,617	20,748	$ 5,885,040		**$ 5,885,040**	$ 6,224,400		**$ 6,224,400**
4	23,666	25,105	18,933	20,084	$ 5,679,840		**$ 5,679,840**	$ 6,025,200		**$ 6,025,200**
5	23,128	24,280	18,502	19,424	$ 5,550,720		**$ 5,550,720**	$ 5,827,200		**$ 5,827,200**
6	22,815	24,094	18,252	19,275	$ 5,475,600		**$ 5,475,600**	$ 5,782,560		**$ 5,782,560**
7	22,608	23,904	18,086	19,123	$ 5,425,920		**$ 5,425,920**	$ 5,736,960		**$ 5,736,960**
8	22,168	23,683	17,734	18,946	$ 5,320,320		**$ 5,320,320**	$ 5,683,920		**$ 5,683,920**
9	22,225	23,611	17,780	18,889	$ 5,334,000		**$ 5,334,000**	$ 5,666,640		**$ 5,666,640**
10	22,269	23,700	17,815	18,960	$ 5,344,560	$ 1,965,920	**$ 7,310,480**	$ 5,688,000	$ 2,090,000	**$ 7,778,000**
11	22,575	23,898	18,060	19,118	$ 5,418,000	$ 1,966,640	**$ 7,384,640**	$ 5,735,520	$ 2,108,400	**$ 7,843,920**
12	22,738	24,067	18,190	19,254	$ 5,457,120	$ 1,961,680	**$ 7,418,800**	$ 5,776,080	$ 2,074,800	**$ 7,850,880**
13	22,922	24,258	18,338	19,406	$ 5,501,280	$ 1,893,280	**$ 7,394,560**	$ 5,821,920	$ 2,008,400	**$ 7,830,320**
14	23,196	24,551	18,557	19,641	$ 5,567,040	$ 1,850,240	**$ 7,417,280**	$ 5,892,240	$ 1,942,400	**$ 7,834,640**
15	23,469	24,825	18,775	19,860	$ 5,632,560	$ 1,825,200	**$ 7,457,760**	$ 5,958,000	$ 1,927,520	**$ 7,885,520**
16	23,755	25,133	19,004	20,106	$ 5,701,200	$ 1,808,640	**$ 7,509,840**	$ 6,031,920	$ 1,912,320	**$ 7,944,240**
17	24,051	25,445	19,241	20,356	$ 5,772,240	$ 1,773,440	**$ 7,545,680**	$ 6,106,800	$ 1,894,640	**$ 8,001,440**
18	24,341	25,755	19,473	20,604	$ 5,841,840	$ 1,778,000	**$ 7,619,840**	$ 6,181,200	$ 1,888,880	**$ 8,070,080**
19	24,679	26,106	19,743	20,885	$ 5,922,960	$ 1,781,520	**$ 7,704,480**	$ 6,265,440	$ 1,896,000	**$ 8,161,440**
20	25,004	26,444	20,003	21,155	$ 6,000,960	$ 1,806,000	**$ 7,806,960**	$ 6,346,560	$ 1,911,840	**$ 8,258,400**
21	25,318	26,780	20,254	21,424	$ 6,076,320	$ 1,819,040	**$ 7,895,360**	$ 6,427,200	$ 1,925,360	**$ 8,352,560**
22	25,586	27,056	20,469	21,645	$ 6,140,640	$ 1,833,760	**$ 7,974,400**	$ 6,493,440	$ 1,940,640	**$ 8,434,080**
23	25,801	27,286	20,641	21,829	$ 6,192,240	$ 1,855,680	**$ 8,047,920**	$ 6,548,640	$ 1,964,080	**$ 8,512,720**
24	25,987	27,476	20,790	21,981	$ 6,236,880	$ 1,877,520	**$ 8,114,400**	$ 6,594,240	$ 1,986,000	**$ 8,580,240**
25	26,112	27,604	20,890	22,083	$ 6,266,880	$ 1,900,400	**$ 8,167,280**	$ 6,624,960	$ 2,010,640	**$ 8,635,600**
26	26,203	27,702	20,962	22,162	$ 6,288,720	$ 1,924,080	**$ 8,212,800**	$ 6,648,480	$ 2,035,600	**$ 8,684,080**

Assumptions:

Cost per Vaccination	$ 300
Cost per Booster Shot	$ 100

Over the quarter century of the program, the annual cost rises from about $12 million to almost $17 million (in constant 2005 CDN dollars). Of course, the biggest jump in costs comes in the year when the booster shot is first administered.

Combining Estimated Program Costs and Potential Medical Costs Avoided

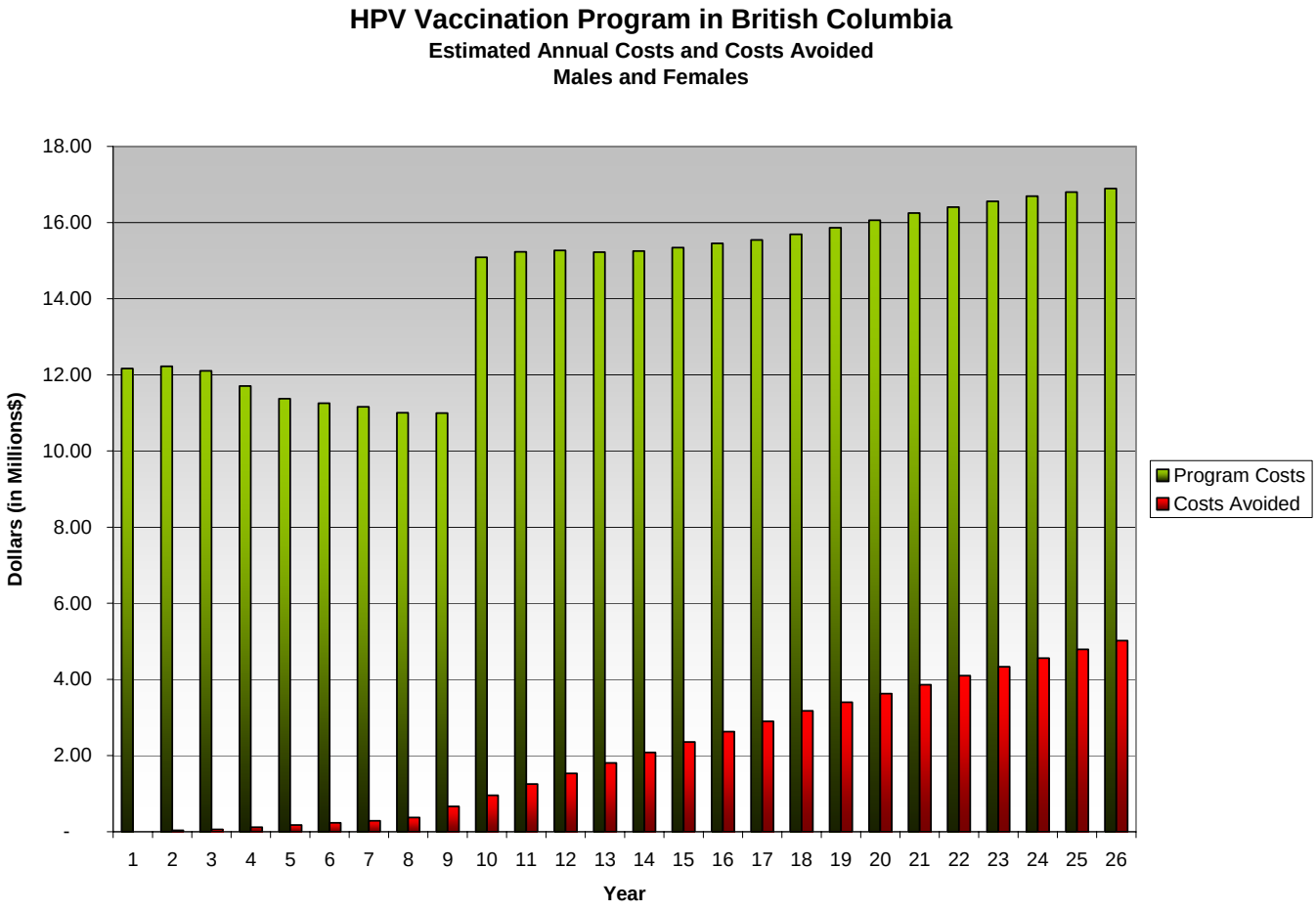
The following table pulls together the costs and effectiveness (as represented by avoided costs) of a vaccination program in B.C.

HPV Vaccination Program in British Columbia
Estimated Annual Costs and Cost Avoided
With HPV 16/18/6/11 Vaccine
(In Constant 2005 Canadian Dollars)

Year	Estimated Vaccination Program Costs			Potential Medical Costs Avoided		
	Females	Males	**Total**	Females	Males	**Total**
1	$ 5,897,760	$ 6,270,000	**$ 12,167,760**	$ -	$ -	**$ -**
2	$ 5,899,920	$ 6,325,200	**$ 12,225,120**	$ 15,308	$ 16,068	**$ 31,376**
3	$ 5,885,040	$ 6,224,400	**$ 12,109,440**	$ 30,622	$ 32,277	**$ 62,899**
4	$ 5,679,840	$ 6,025,200	**$ 11,705,040**	$ 69,599	$ 50,707	**$ 120,305**
5	$ 5,550,720	$ 5,827,200	**$ 11,377,920**	$ 108,051	$ 68,648	**$ 176,699**
6	$ 5,475,600	$ 5,782,560	**$ 11,258,160**	$ 146,109	$ 86,041	**$ 232,150**
7	$ 5,425,920	$ 5,736,960	**$ 11,162,880**	$ 183,147	$ 103,242	**$ 286,388**
8	$ 5,320,320	$ 5,683,920	**$ 11,004,240**	$ 235,482	$ 137,198	**$ 372,680**
9	$ 5,334,000	$ 5,666,640	**$ 11,000,640**	$ 464,033	$ 201,535	**$ 665,568**
10	$ 7,310,480	$ 7,778,000	**$ 15,088,480**	$ 692,446	$ 265,804	**$ 958,249**
11	$ 7,384,640	$ 7,843,920	**$ 15,228,560**	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 7,418,800	$ 7,850,880	**$ 15,269,680**	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 7,394,560	$ 7,830,320	**$ 15,224,880**	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 7,417,280	$ 7,834,640	**$ 15,251,920**	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 7,457,760	$ 7,885,520	**$ 15,343,280**	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 7,509,840	$ 7,944,240	**$ 15,454,080**	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 7,545,680	$ 8,001,440	**$ 15,547,120**	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 7,619,840	$ 8,070,080	**$ 15,689,920**	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 7,704,480	$ 8,161,440	**$ 15,865,920**	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 7,806,960	$ 8,258,400	**$ 16,065,360**	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 7,895,360	$ 8,352,560	**$ 16,247,920**	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 7,974,400	$ 8,434,080	**$ 16,408,480**	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 8,047,920	$ 8,512,720	**$ 16,560,640**	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 8,114,400	$ 8,580,240	**$ 16,694,640**	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 8,167,280	$ 8,635,600	**$ 16,802,880**	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 8,212,800	$ 8,684,080	**$ 16,896,880**	$ 3,623,677	$ 1,398,243	**$ 5,021,920**
Total	**$ 181,451,600**	**$ 192,200,240**	**$ 373,651,840**	**$ 39,334,643**	**$ 14,991,731**	**$ 54,326,374**

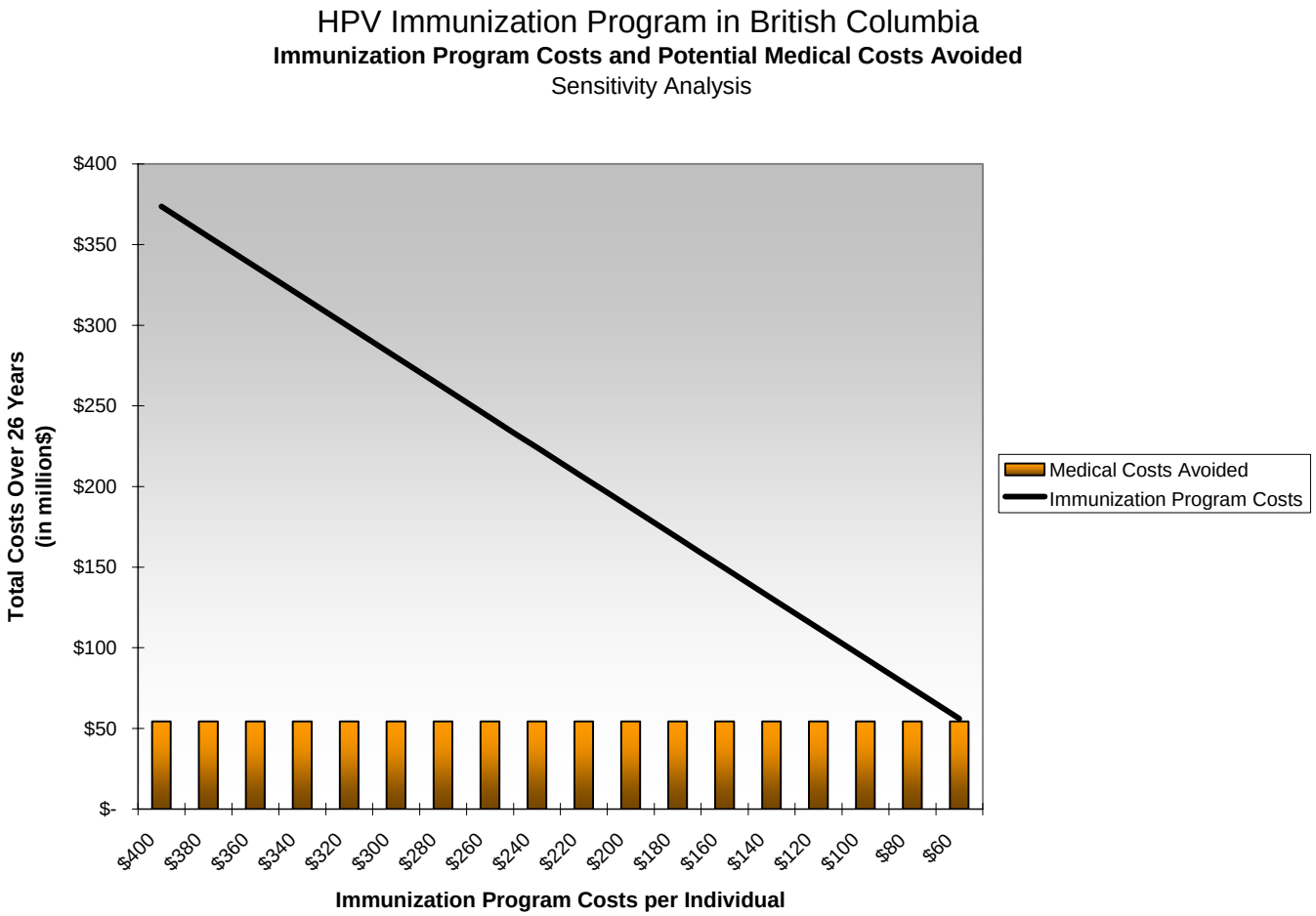
It becomes quickly apparent that there is a wide gap between the expense of a vaccination program (under the given assumptions) and the direct medical costs avoided. The ratio of these two figures (expense : avoided cost) does improve, from 0.003 in year 2 to 0.297 in year 26, holding out hope that there might be a better financial balance over the projected lifetime of a 12 year old (though it is difficult to imagine even the undiscounted cumulative costs ever being "recovered"). In any event, no matter how favourable a 40 or 50 year projection might be, a quarter century is already a long time to assume static conditions in any model; it would be difficult to have confidence in longer projections.

The results presented in the preceding table are shown graphically on the following chart.


HPV Vaccination Program in British Columbia
Estimated Annual Costs and Costs Avoided
Males and Females
Dollars (in Millionss$)
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Year
Program Costs
Costs Avoided

Sensitivity Analysis

A key issue in the analysis is the cost per individual of the HPV immunization program. While the initial estimate is $400 (including the booster shot) we varied these costs from $60 to $400. The following chart provides a summary of the estimated total medical costs avoided ($54.3 million) over a 26 year period in comparison to the total immunization program costs during the same time period if the cost per individual of the vaccinations is varied from $60 to $400.



From a strict medical-cost perspective, the program 'breaks even' when immunization costs are reduced to $60 per individual.

Key Issues

It has become apparent in this report that evaluating the introduction of a vaccination program involves a complex set of factors and assumptions. While we have addressed and incorporated many of these, several issues and questions remain for ongoing consideration.

- What is the best setting for the program? School-based vaccination programs have a much higher success rate than those pursued in traditional health care settings.

- Targeting high risk groups may be more cost-effective, but these groups tend to be the hardest to reach. As well, the relevant risk factors may not be easy to detect.

- Why vaccinate 12 year old girls? A study by the US Centers for Disease Control indicated that 3% of girls have had sexual intercourse by age 13, 18.6% by age 15, and 59.2% by age 18. A reasonable goal may be to catch virtually all females before they have any sexual contact.

- Should both boys and girls be vaccinated? As we indicated earlier, some modelling has questioned the cost-effectiveness of extending HPV vaccines to males. However, it may be easier to have population acceptance if both males and females participate in a vaccination program.

- Will parental consent be required or will a vaccination program be part of public health policy? If parental consent is required, how many parents will agree to have their 12 year old daughters vaccinated against a sexually transmitted disease? And how can this proportion be increased through educational and other means?

- How might screening costs in the population be reasonably reduced over the course of a vaccination program?

- How will patterns of transmission and HPV infection change in the future, especially in the light of co-infections with viruses such as HIV?

- Is there an advantage to going beyond a quadrivalent vaccine and target even more types? What would this cost and how long would trials take?

- Women who are vaccinated would be expected to reduce their participation in screening programs, thus potentially offsetting some of the costs of the vaccination program. Some continued participation, but at less frequent intervals, would be expected and encouraged. What would the potential extent of savings due to reduced screening be?

Introduction

Purpose

The fact that viral infections can cause cancer has been suspected for over a 100 years, beginning with the observed association between cervical cancer and multiple sexual partners. Intense research in recent years has identified that 90% or more of cervical cancers can be traced to human papillomavirus (HPV) types 16 and 18, plus another dozen probable types. This conclusion is unique in cancer research; no other cancer in humans has been shown to have such a clear and necessary cause. This has afforded an unprecedented opportunity for cancer control. Of additional interest in any immunization program is the fact that some HPV types, while showing low oncogenic risk, do produce genital warts, which by themselves add to the number and cost of outpatient clinic visits in developed nations.

There are three basic approaches to preventing cancer development with any virus, including HPV:

1. Preventing exposure to the pathogen in the first place.

2. Preventing establishment of infection, especially through vaccination.

3. Preventing full cancer development once infection is present (including detecting and treating the infection or precancerous cells and lesions before cancer becomes completely established).

The traditional prevention focus with HPV and cervical cancer has involved the last category. Screening (particularly via the well-known Pap smear) has been extremely successful in reducing the incidence of cervical cancer in developed countries over the last 50 years. Even before considering new frontiers of care, it must be recognized that screening itself is not a static topic. For instance, the recent exploration of HPV DNA testing has both expanded and complicated the prevention field with respect to cervical cancer.

Alongside developments in screening technology, the greatest excitement in the last decade has been in “category two” preventive approaches, especially vaccines. The drive towards a safe and effective HPV vaccine has been intense, with two pharmaceutical companies in the final trial phase. The licensing and deployment of very promising candidate vaccines may be only a few years away.

The main question for *developed* countries is whether or not a public health regimen that includes a vaccination program would be cost effective and even superior to other prevention scenarios. Answering this is the key focus for this position paper, as applied to the British Columbia setting. Secondary issues to be explored in general and, as appropriate, in the B.C. context include:

- the “state of the art” of HPV science, epidemiology and health care
- current and emerging vaccine types
- trial results to date
- the value and limitation of modeling disease natural history
- projected effectiveness of disease reduction with immunization
- vaccine safety profile
- potential protocols for targeting populations

- integration of immunization with other prevention approaches
- (if indicated) implementation steps and challenges
- future developments.

More specifically, the following questions will be addressed in this position paper:

1. Would a HPV immunization program in B.C. be cost-effective?
2. How many cancers (cervical, anogenital, head and neck, etc.) might be prevented by such a program?
3. What are the expected side-effects of such an immunization program, e.g., potential toxicities?
4. Should such a program be implemented in B.C.?
5. If so, should it be implemented in targeted special populations or be population-wide?

Background

The human papillomavirus represents a bewildering array of types, subtypes and variants. Over 100 HPV types have been identified so far, with approximately 40 known to infect the human genital tract.[1] Of these, about half are oncogenic, with the majority of cancer-causing forms related genetically to two main types, HPV 16 and HPV 18.[2,3] Indeed, the latter two types together account for about 70% of cervical cancer cases (an increase from earlier estimates of 50%).[4,5,6]

Besides cervical cancers, HPV types have been implicated in a number of other cancers, including anogenital carcinomas, e.g., of the vagina, vulva, or penis,[7] and various nongenital mucosal and cutaneous diseases, e.g., head and neck cancers.[8,9] A particularly significant cancer related to HPV in high-risk male populations is squamous cell anal carcinoma.[10] Aside from precancerous lesions and full cancers, the other main disorders associated with HPV are different types of genital warts and recurrent respiratory papillomatosis.

Transmission of the Agent

The primary mode of genital HPV transmission is sexual intercourse. In fact, taken as a group, anogenital HPV is the most common sexually transmitted infection.[11] The lifetime risk of contracting such an infection is about 80%.[12]

Studies show that the number of recent sexual partners is significantly associated with the incidence of HPV infection.[13,14] Limited research has concluded that the

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[1] Some researchers are reporting that there are approximately 200 different subtypes; the number may depend on the definition of what constitutes a new type. Munger K, Baldwin A, Edwards KM et al. Mechanisms of human papillomavirus-induced oncogenesis. *Journal of Virology.* 2004; 78(21): 11451-60.

[2] Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine.* 2003; 348(6): 518-27.

[3] Bosch FX, Manos MM, Munoz N et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *Journal of the National Cancer Institute.* 1995; 87(11): 796-802.

[4] Clifford GM, Smith JS, Plummer M et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *British Journal of Cancer.* 2003; 88(1): 63-73.

[5] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer.* 2003; 106(6): 896-904.

[6] Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *The Lancet.* 2004; 364(9447): 1757-65.

[7] Dillner J, Meijer CJ, von Krogh G et al. Epidemiology of human papillomavirus infection. *Scandinavian Journal of Urology & Nephrology Supplement.* 2000; 34(205): 194-200.

[8] Mork J, Lie AK, Glattre E et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine.* 2001; 344(15): 1125-31.

[9] Gillison ML, Koch WM, Capone RB et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *Journal of the National Cancer Institute.* 2000; 92(9): 709-20.

[10] Xi LF, Critchlow CW, Wheeler CM et al. Risk of anal carcinoma in situ in relation to human papillomavirus type 16 variants. *Cancer Research.* 1998; 58(17): 3839-44.

[11] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.

[12] Bekkers RL, Massuger LF, Bulten J et al. Epidemiological and clinical aspects of human papillomavirus detection in the prevention of cervical cancer. *Reviews in Medical Virology.* 2004; 14(2): 95-105.

virus can be passed through fomites (substances or articles that hold and convey infection, e.g., handkerchief) or skin contact, but the clinical significance of this potential mode of transmission remains very debatable; no evidence of such transmission has been found in the case of genital lesions, the precursor to cancer.[15] A final, plausible transmission route implicated is non-penetrative sexual activity (including oral sex).[16] Although the whole topic of transmission is subject to ongoing study, the basic understanding is that HPV infections are "easily transmitted."[17]

Although earlier studies suggested the possibility of "vertical transmission" of HPV from mother to infant during delivery, more recent research has concluded that this route of viral spread is very low-risk.[18,19] Even when the virus is found in newborns, it often seems to clear after a few months.[20] As Arena and co-authors noted, "the data reported in the literature on the relationship between HPV and pregnancy are highly discordant."[21] The first report has recently been made of fetal cervical HPV infection through *intrauterine* exposure.[22]

Co-factors and Correlates

HPV infection is very common, but mostly transient. The fact that only a certain fraction of women with persistent HPV infection will eventually develop cervical cancer indicates that the virus, though necessary, is not always a sufficient cause. Co-factors seem to be involved in at least some cervical carcinogenesis.[23] For example, risk for cervical cancer developing with HPV infection increases twofold when the woman is or has been a smoker;[24] recently, evidence for the effect of passive

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[13] Sellors JW, Karwalajtys TL, Kaczorowski J et al. Incidence, clearance and predictors of human papillomavirus infection in women. *Canadian Medical Association Journal.* 2003; 168(4): 421-5.
[14] Kjaer SK, Chackerian B, van den Brule AJ et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiology, Biomarkers & Prevention.* 2001; 10(2): 101-6.
[15] Bruck LR, Zee S, Poulos B et al. Detection of cervical human papillomavirus infection by in situ hybridization in fetuses from women with squamous intraepithelial lesions. *Journal of Lower Genital Tract Disease.* 2005; 9(2): 114-7.
[16] Winer RL, Lee SK, Hughes JP et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *American Journal of Epidemiology.* 2003; 157(3): 218-26.
[17] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.
[18] Smith EM, Ritchie JM, Yankowitz J et al. Human papillomavirus prevalence and types in newborns and parents: concordance and modes of transmission. *Sexually Transmitted Diseases.* 2004; 31(1): 57-62.
[19] Watts DH, Koutsky LA, Holmes KK et al. Low risk of perinatal transmission of human papillomavirus: results from a prospective cohort study. *American Journal of Obstetrics & Gynecology.* 1998; 178(2): 365-73.
[20] Arena S, Marconi M, Ubertosi M et al. HPV and pregnancy: diagnostic methods, transmission and evolution. *Minerva Ginecologica.* 2002; 54(3): 225-37.
[21] Arena S, Marconi M, Ubertosi M et al. HPV and pregnancy: diagnostic methods, transmission and evolution. *Minerva Ginecologica.* 2002; 54(3): 225-37.
[22] Bruck LR, Zee S, Poulos B et al. Detection of cervical human papillomavirus infection by in situ hybridization in fetuses from women with squamous intraepithelial lesions. *Journal of Lower Genital Tract Disease.* 2005; 9(2): 114-7.
[23] Munoz N. Human papillomavirus and cancer: the epidemiological evidence. *Journal of Clinical Virology.* 2000; 19(1-2): 1-5.
[24] Plummer M, Herrero R, Franceschi S et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case--control study. *Cancer Causes Control.* 2003; 14(9): 805-14.

smoking has also been reported.[25,26] In fact, some research suggests that exposure to cigarette smoke may be *required* as a carcinogen to advance HPV-infected cells toward high-grade neoplasms.[27] The crucial biological pathway appears to involve the oxidant load created through smoking, though this remains a matter of investigation.[28,29]

There is evidence that the presence of other sexually transmitted agents, cervical inflammation, multiple births (or multiparity), and long-term oral contraceptive use all correlate with progression towards cervical cancer.[30,31,32,33] Although a causal relationship is unproven, herpes simplex virus-2 may act in conjunction with HPV to create cervical cancer (possibly multiplying the risk of developing the main types of cervical cancer up to 2 or 3 times).[34] HIV (with its associated immune suppression) and *Chlamydia trachomatis* are also on the list of potential co-factors.[35,36,37,38,39]

Natural History and Carcinogenesis

This section will focus on the main HPV-related cancer of interest to public health, namely, cervical cancer. This type of cancer arises through three carcinogenic steps. First, HPV infection of the cervix occurs, probably as a result of sexual intercourse.

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[25] Trimble CL, Genkinger JM, Burke AE et al. Active and passive cigarette smoking and the risk of cervical neoplasia. *Obstetrics & Gynecology.* 2005; 105(1): 174-81.
[26] Tay SK, Tay KJ. Passive cigarette smoking is a risk factor in cervical neoplasia. *Gynecologic Oncology.* 2004; 93(1): 116-20.
[27] Ho GY, Kadish AS, Burk RD et al. HPV 16 and cigarette smoking as risk factors for high-grade cervical intra-epithelial neoplasia. *International Journal of Cancer.* 1998; 78(3): 281-5.
[28] Giuliano A. Cervical carcinogenesis: the role of co-factors and generation of reactive oxygen species. *Salud Publica de Mexico.* 2003; 45 Suppl 3: S354-60.
[29] Moore TO, Moore AY, Carrasco D et al. Human papillomavirus, smoking, and cancer. *Journal of Cutaneous Medicine & Surgery.* 2001; 5(4): 323-8.
[30] Castellsague X, Bosch FX, Munoz N. Environmental co-factors in HPV carcinogenesis. *Virus Research.* 2002; 89(2): 191-9.
[31] Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *Journal of the National Cancer Institute Monograph.* 2003; (31): 20-8.
[32] Munoz N, Franceschi S, Bosetti C et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1093-101.
[33] Moreno V, Bosch FX, Munoz N et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1085-92.
[34] Smith JS, Herrero R, Bosetti C et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *Journal of the National Cancer Institute.* 2002; 94(21): 1604-13.
[35] de Sanjose S, Palefsky J. Cervical and anal HPV infections in HIV positive women and men. *Virus Research.* 2002; 89(2): 201-11.
[36] La Ruche G, You B, Mensah-Ado I et al. Human papillomavirus and human immunodeficiency virus infections: relation with cervical dysplasia-neoplasia in African women. *International Journal of Cancer.* 1998; 76(4): 480-6.
[37] Weissenborn SJ, Funke AM, Hellmich M et al. Oncogenic human papillomavirus DNA loads in human immunodeficiency virus-positive women with high-grade cervical lesions are strongly elevated. *Journal of Clinical Microbiology.* 2003; 41(6): 2763-7.
[38] Palefsky JM, Holly EA. Chapter 6: Immunosuppression and co-infection with HIV. *Journal of the National Cancer Institute Monograph.* 2003; (31): 41-6.
[39] Smith JS, Munoz N, Herrero R et al. Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. *Journal of Infectious Diseases.* 2002; 185(3): 324-31.

The effect of infection on cervical cells is quite variable. Whatever the impact, most infections tend to resolve over a one- to two-year period.[40]

The next step, progression to a precancerous state, happens in a small percentage of cases. The crucial factor is the persistence of HPV, i.e., when clearance is incomplete. Persistence is due mostly to some capability of the virus to suppress or evade the body's natural immune system.[41,42]

The modal time between HPV infection (most often in late teens or early 20s) and the peak of precancer development is 7 to 10 years. This places the typical age of women with precancerous lesions at about 30 years. The final step is full-blown, invasive cancer, which may take another 10 years to develop; between one-third and two-thirds of women with precancer will move on to this end-point.

In sum, this generic picture of a prolonged natural history confirms the basic understanding that rapidly invasive cancers among *young* women are rare events.[43]

Preventive Interventions

There are three approaches to preventing cancer with an infectious origin: limiting exposure to the pathogen in the first place; interrupting the establishment of infection; and stopping full cancer development once infection is present.

The most "full-proof" way to eliminate the risk for future genital HPV infections is to refrain from genital contact with another person. The next most certain approach is to only be sexually active within a long-term, mutually monogamous relationship with an uninfected partner.[44] Indeed, reducing the number of potentially risky sexual partners by any means is clearly a preventive measure. These sort of proactive "partner management" interventions become even more important in light of the fact that the ability to prevent transmission through condom use has not been demonstrated (though condoms may protect against the development of genital warts and lesions).[45,46]

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[40] Schiffman MH, Castle P. Epidemiologic studies of a necessary causal risk factor: human papillomavirus infection and cervical neoplasia. *Journal of the National Cancer Institute.* 2003; 95(6): E2.

[41] Frazer IH, Thomas R, Zhou J et al. Potential strategies utilised by papillomavirus to evade host immunity. *Immunological Reviews.* 1999; 168: 131-42.

[42] Padilla-Paz LA. Human papillomavirus vaccine: history, immunology, current status, and future prospects. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 226-40.

[43] Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monograph.* 2003; (31): 14-9.

[44] *Report to Congress: Prevention of Genital Human Papillomavirus Infection.* Centers for Disease Control and Prevention; 2004. Available at http://www.cdc.gov/std/HPV/2004HPV%20Report.pdf. Accessed May 2005.

[45] Giles S. Transmission of HPV. *Canadian Medical Association Journal.* 2003; 168(11): 1391; author reply.

[46] Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases.* 2002; 29(11): 725-35.

The one-to-one association of cervical cancer and HPV infection has two practical implications for prevention: enhanced screening programs based on HPV testing and the development of a vaccine.[47]

Screening Programs

Conventional cervical cancer screening has a much longer history than the development of vaccines or HPV DNA testing. Cancer screening is designed to detect the presence of precancerous cells or lesions and prompt preventive measures. By identifying the precursor lesions associated with HPV infection, screening programs based on the techniques of cytology[48] have reduced the incidence of invasive cervical cancer. One UK report concluded that cervical cancer screening had prevented an epidemic that would have killed about 1 in 65 British women born since 1950, or about 6,000 deaths per year. In sum, at least 100,000 women born between 1951 and 1970 have been spared premature death in that country.[49] Even with such dramatic statistics, cost-effectiveness analyses of such programs have produced variable results. In countries where an abnormal test result can lead to substantial resources being invested in follow-up management, the cost per life year saved may run into many thousands of dollars.[50]

The most common screening test that goes beyond a regular gynaecologic examination is the so-called Pap smear, an abbreviation of the name of its originator, GN Papanicolaou.[51] He published a cornerstone paper in 1941 which demonstrated a correlation between abnormalities in scraped cells and cervical cancer. The aim, and the eventual result, of a simple screening test was to save "millions of women who would otherwise discover their cancer of the cervix uteri at a non-curable stage."[52] As described earlier, precursor lesions usually appear a considerable length of time before a carcinoma; thus early detection and prompt management can lead to effective prevention of the disease.

The Pap smear is a screening rather than a diagnostic test. This means that any abnormal cells (so-called cervical intraepithelial neoplasia, or CIN) need to be followed up, starting with further examinations or tests (e.g., via a colposcopy) to evaluate whether cancer itself is present or threatening.

An abnormal Pap smear can be treated in a variety of ways, from conservative monitoring over a period of months to see if it returns to normal, to cryosurgery that freezes and destroys infected cells, to other procedures that excise problem tissue.

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[47] Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus Research.* 2002; 89(2): 183-90.
[48] The examination of cellular structure.
[49] Peto J, Gilham C, Fletcher O et al. The cervical cancer epidemic that screening has prevented in the UK. *The Lancet.* 2004; 364(9430): 249-56.
[50] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[51] Alternate terminology includes PAP Test, Papanicolaou smear, cervical smear, cervical/vaginal cytology.
[52] Michalas SP. The Pap test: George N. Papanicolaou (1883-1962). A screening test for the prevention of cancer of uterine cervix. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2000; 90(2): 135-8.

The main strategic issues with Pap smears are:

- Identifying the most efficient age cut-offs and frequency of routine testing.
- Employing an organized program or more opportunistic screening.[53]
- Introducing automatic scanning devices.[54]
- How and when to integrate HPV DNA testing. The most common proposal is a primary Pap test with an adjunctive HPV test, especially if the cytological examination provides equivocal results.[55]
- Establishing the best protocol for monitoring tissue status after precancer intervention. A meta-analysis of the literature suggested that a double negative (i.e., no abnormality in Pap smear or HPV DNA test) at 6 months and then again at 24 months is sufficient to allow the person to return to a routine testing protocol.[56]

Despite the amazing track record of Pap smears, the motivation to also move towards HPV DNA testing and / or vaccinations has emerged due to the high false-negatives seen in conventional testing. The false-negative rate with Pap smears ranges from 5 to 30%.[57] This results in about half of the cervical cancer cases in the US, for example, occurring in those who are routinely screened; this affects about 7000 women per year. Cervical adenocarcinomas[58] in younger women are especially hard to detect and prevent.[59] All of this uncertainty has prompted a large amount of litigation and huge awards. False positives with Pap smears are also a concern; in fact, much anxiety is produced by any kind of positive test, a burden of sometimes questionable value given that the vast majority of HPV infections resolve spontaneously. Of course, the challenge of managing positive results would also apply to the newer HPV tests.

We may be at the limit of human ability to derive appropriate and consistent information from the microscopic examination of Pap specimens. Thus, efforts to increase the sensitivity of the test have focused more on the collection, handling and processing of specimens. So called thin-layer (or liquid-based) technology involves collecting material with a soft brush and then rinsing it into a special fluid preservative; from there, a thin-layer slide can be prepared which offers several

[53] Gustafsson L, Ponten J, Zack M et al. International incidence rates of invasive cervical cancer after introduction of cytological screening. *Cancer Causes Control.* 1997; 8(5): 755-63.
[54] Nieminen P, Vuorma S, Viikki M et al. Comparison of HPV test versus conventional and automation-assisted Pap screening as potential screening tools for preventing cervical cancer. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2004; 111(8): 842-8.
[55] Vassilakos P, de Marval F, Munoz M et al. Human papillomavirus (HPV) DNA assay as an adjunct to liquid-based Pap test in the diagnostic triage of women with an abnormal Pap smear. *International Journal of Gynecology & Obstetrics.* 1998; 61(1): 45-50.
[56] Zielinski GD, Bais AG, Helmerhorst TJ et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. *Obstetrical & Gynecological Survey.* 2004; 59(7): 543-53.
[57] Foulks MJ. The Papanicolaou smear: its impact on the promotion of women's health. *Journal of Obstetric, Gynecologic & Neonatal Nursing.* 1998; 27(4): 367-73.
[58] A cancer that develops in the lining or inner surface of an organ. As opposed to, for instance, cancer in squamous epithelial cells.
[59] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.

improvements in terms of the quality of the cytological examination. This method has the advantage of providing material for any subsequent HPV DNA test as well.[60]

Whatever the risk, inconvenience and cost of false negatives, there is a tragic irony developing around looking for a "perfect" Pap smear: it may become too good to be affordable. The cost of more specialized specimen collection and preparation, computerized rescreening, and malpractice insurance could replace an inexpensive, widely available Pap smear. The reduced availability of testing that may result would "undoubtedly lead to increased cervical carcinoma."[61] The fact is that more women experience the development of cancer because of the failure to have a regular Pap smear than because of errors in cytodiagnosis.[62]

HPV DNA Testing

There is a lot of debate concerning the potential usefulness of augmenting (or even replacing) conventional cytological screening for cervical cancer with an HPV DNA test. As one study noted, "the extreme rarity of HPV-negative cancers reinforces the rationale for HPV testing in addition to, or even instead of, cervical cytology in routine cervical screening."[63] Additional pressure to consider alternatives comes from the challenges and deficiencies of current routine screening methods. However, the extra cost of HPV testing is viewed by some authorities as being prohibitive.

In April, 2005, the American College of Obstetricians and Gynecologists released a practice bulletin that acknowledges the high sensitivity of HPV DNA testing in terms of ruling out cervical cancer.[64] If HPV is not present, women can be reassured with a large degree of certainty that they are cancer-free. Using the test in the opposite direction is where the problems begin, i.e., deciding whether a detected HPV infection (even high risk types) but *without* cervical abnormality should be followed and treated (and, if so, when and how).[65] The cost of any additional surveillance (required in about 4 to 6% of the screened population) adds to the already higher expense of HPV testing.[66] On the other hand, women with normal cytology and negative for high-risk HPV types can be screened less frequently; cost-effectiveness and modeling studies suggest that this fact could offset increased costs with HPV testing and thus make the procedure attractive from a public health perspective.[67] A comprehensive review of the literature up to 2005 confirmed that adding HPV testing to conventional screening would "likely" be cost-effective, though it also

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[60] Michalas SP. The Pap test: George N. Papanicolaou (1883-1962). A screening test for the prevention of cancer of uterine cervix. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2000; 90(2): 135-8.

[61] DeMay RM. Common problems in Papanicolaou smear interpretation. *Archives of Pathology & Laboratory Medicine.* 1997; 121(3): 229-38.

[62] Boronow RC. Death of the Papanicolaou smear? A tale of three reasons. *American Journal of Obstetrics & Gynecology.* 1998; 179(2): 391-6.

[63] Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 1999; 189(1): 12-9.

[64] Summary available at http://investor.digene.com/phoenix.zhtml?c=82439&p=irol-newsArticle_Print&ID=695453&highlight=. Accessed June 2005.

[65] Franceschi S, Mahe C. Human papillomavirus testing in cervical cancer screening. *British Journal of Cancer.* 2005; 92(9): 1591-2.

[66] Cuzick J, Szarewski A, Cubie H et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *The Lancet.* 2003; 362(9399): 1871-6.

[67] Brink AA, Zielinski GD, Steenbergen RD et al. Clinical relevance of human papillomavirus testing in cytopathology. *Cytopathology.* 2005; 16(1): 7-12.

acknowledged that "further research is needed into the practicalities of implementing such a policy."[68]

Another potential area of usefulness for HPV testing is rapid intermediate evaluation of precancer treatments.[69,70,71] This must be contrasted with alternate approaches to tracking the development of disease and the effectiveness of therapy based on surveillance of molecular biomarkers associated with the natural history of HPV-related carcinogenesis.[72]

A New Horizon

As we have noted above, the frontier in HPV-related disease is the potential use of prophylactic vaccines to control HPV infection and therapeutic vaccines to treat associated lesions. The main targets of interest in vaccine development have been the key oncoproteins responsible for malignant transformation.[73] Results from small phase I trials were variable.[74] However, if the promise seen in some more recent studies (see the major section below) is fulfilled, then vaccines may end up playing a vital role in both primary and secondary prevention of cervical cancer.

Before investigating the current research on HPV vaccines in more detail, we will first examine the clinical burden of HPV infection, including the relationship between specific sub-types of HPV infection and specific diseases, as well as the cost of treating these HPV-related diseases.

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[68] Holmes J, Hemmett L, Garfield S. The cost-effectiveness of human papillomavirus screening for cervical cancer. A review of recent modelling studies. *European Journal of Health Economics.* 2005; 6(1): 30-7.

[69] Elfgren K, Jacobs M, Walboomers JM et al. Rate of human papillomavirus clearance after treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology.* 2002; 100(5 Pt 1): 965-71.

[70] Paraskevaidis E, Arbyn M, Sotiriadis A et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. *Cancer Treatment Reviews.* 2004; 30(2): 205-11.

[71] Bodner K, Bodner-Adler B, Wierrani F et al. Is therapeutic conization sufficient to eliminate a high-risk HPV infection of the uterine cervix? A clinicopathological analysis. *Anticancer Research.* 2002; 22(6B): 3733-6.

[72] Padilla-Paz LA. Emerging technology in cervical cancer screening: status of molecular markers. *Clinical Obstetrics & Gynecology.* 2005; 48(1): 218-25.

[73] Peng S, Ji H, Trimble C et al. Development of a DNA vaccine targeting human papillomavirus type 16 oncoprotein E6. *Journal of Virology.* 2004; 78(16): 8468-76.

[74] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.

The Clinical Burden of HPV Infection

A Note on Cancer Types, Grades and Staging

The term cancer usually is reserved for a condition where cells are proliferating in an abnormal and uncontrolled way and invading (or threatening to invade) beyond the location where atypical cells first developed. Atypical cells or tissue may not become cancerous (or malignant); thus they are sometimes referred to as a *precancerous* lesion. Other important terms denoting abnormal cellular changes or growth, whether benign or malignant, include tumour, neoplasia (or neoplasm) and dysplasia.

Cancer comes in different forms and intensities. Carcinomas affect squamous epithelial cells, the keratinocytes. Squamous cells are the cells that make up most of the skin (epithelium). Thus, an important term in cancer terminology is *intraepithelial*; this refers to cancer within or among the layer of cells that cover body surfaces and line cavities, ducts, organs and vessels. *Invasive* cancer invades into the dermis below the epidermis.

The various characterizations described above are sometimes combined in descriptions specific to cancer sites, e.g., vulvar squamous cell carcinoma (VSCC); cervical intraepithelial neoplasia (CIN). The technical term for cancer itself is malignant neoplastic disease.

Cancer Types

Other histologic types of epithelial cancers (or carcinomas) include:

- *verrucous carcinoma*, a variety of squamous cell carcinoma with a papillary or wartlike appearance (especially seen in the oral mucosa).
- *basaloid carcinoma*, also a variant of squamous cell carcinoma.
- *adenocarcinoma*, a cancer that develops in the lining or inner surface of an organ, and often involves secreting or glandular cells.
- *basal cell carcinoma*, a type of skin cancer that arises from the basal cells; small round cells found in the lower part (or base) of the epidermis.

Identifying the anatomical site of the cancer is also important, including where it begins; the site of origin involves a primary cancer, e.g., a *primary* vaginal cancer begins in the vagina. The term *secondary* is applied to cancers which have spread from another location, e.g., secondary vaginal cancer may have originated in the cervix or vulva.

Beyond the tissue and site categories for cancer, precancerous changes and actual cancers are commonly described in terms of tumour *grades* and clinical *stages.*

Cancer Grades

Grades represent a subjective summary of how tumourous tissue looks under microscopic examination; they serve to mark the *gradation* from precancerous cells to invasive cancer. The most common grading system, used with a number of cancer types (in particular, squamous cell carcinoma), is based on four levels. Grade 1 tumours have cells that look very much like normal cells, i.e., abundant cytoplasm, keratin and so on, whereas grade 4 tumours have smaller cells which show little differentiation, i.e., bearing no resemblance to the tissue of origin. Generally, the

higher the grade (or the less differentiated), the more aggressive and less sensitive to treatment the tumour will be; a tumour grade of 4 probably represents a condition which has progressed to at least stage 0 cancer (also known as in-situ carcinoma—see below). The movement from precancerous neoplasia to full cancer is clearly a matter of gradual transition rather than discrete, stepwise jumps.

The grades are often combined with the types and sites of cancer to create various descriptions (and their abbreviations), e.g., a low-grade squamous epithelial lesion (LSIL or LGSIL), which is roughly the same as the following concepts: mild dysplasia, cervical intraepithelial neoplasia, grade 1(CIN 1) and, at least according to some definitions, atypical squamous cells of undetermined significance (ASC-US)—the latter two terms being specific to the cervix. On the other end of the spectrum, a high-grade squamous epithelial lesion (HSIL, HGSIL), or severe dysplasia, equates, in the case of the cervix, to CIN 3. This grade of tumour, technically, is still not cancer per se, though, confusingly, some new systems do label preinvasive or in-situ carcinomas as CIN 3; the scale for anal cancer even refers to "microinvasion" of the tumour as part of the scenario for anal intraepithelial neoplasia (AIN) 3. The flexibility of labels further underlines that grading continues to be a subjective and variable tool in the hands of different clinicians, and a moving target as the best approach to expert and patient communication remains under development.

Cancer Staging

The staging scale is similar to standard grading, in that it involves 4 main levels, I to IV, as well as a stage 0. When clinicians opt to use *Roman* numerals for the grades noted earlier, it can become very confusing to the non-expert; it is important to remember that CIN III, for instance, refers to a tumour grade and not a cancer stage. Unlike grading systems, which are sometimes similar across a number of cancers, staging descriptions are always very specific to the cancer type and / or site. In general terms, stage 0 represents a tumour in-situ, an early cancer that has not invaded beyond the layer of cells in which it began. As one "progresses" through the various stages, the cancer becomes more widespread in lymph nodes and other tissues beyond the original site (a process known as metastasis).

"Competing" staging systems sometimes exist in clinical practice. Happily, there is good consistency between the two main systems used with gynaecological cancers (which dominate the first part of the HPV-related cancer story, as seen below).[75]

[75] Benedet JL, Pecorelli S. Why cancer staging? *International Journal of Gynaecology & Obstetrics.* 2003; 83 Suppl 1: 3.

Malignant Diseases

Cancer of the Cervix

Description
The cervix is the lower third of the uterus; roughly cylindrical in shape, it communicates with the vagina through an orifice called the external os. Cervical cancer is the most prevalent and the most studied form of HPV-related cancer; as such, it has been paradigmatic in research on HPV-mediated tumorigenesis.[76] The cancers of the cervix mainly include carcinomas, especially squamous cell carcinoma (80 to 90% of cases) and adenocarcinomas.[77,78,79]

In the developed world, precancerous lesions in the cervix are usually detected by the well-known Pap smear and related tests. Research and discussions are ongoing concerning the optimum interval between cervical cancer screenings.[80] At the same time, consensus guidelines are becoming established for managing women with confirmed neoplasia.[81,82] Focused treatment is certainly recommended for high-grade squamous epithelial lesions (HSILs), usually excision or other form of ablation of the affected tissue.

Proactive cytology screening and management has contributed to a significant decline in overall cervical cancer incidence and mortality in the last 50 years, though the downward trend seems to have flattened recently.[83,84] In fact, the mortality rate in the US has remained virtually unchanged since the mid-1980s. Reasons for the "plateauing" include increasing numbers of high-risk women who are not regularly screened and sexual activity at a younger age.[85] Another anomaly noted in US statistics is the recent increases in incidence of cervical adenocarcinomas among younger women.[86,87] The trends beyond North America also require surveillance; for

[76] Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. *Journal of the National Cancer Institute Monographs.* 2003; (31): 57-65.
[77] Brinton LA, Fraumeni JF, Jr. Epidemiology of uterine cervical cancer. *Journal of Chronic Diseases.* 1986; 39(12): 1051-65.
[78] Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology.* 2002; 41(3): 185-207.
[79] Andersson S, Larson B, Hjerpe A et al. Adenocarcinoma of the uterine cervix: the presence of human papillomavirus and the method of detection. *Acta Obstetricia et Gynecologica Scandinavica.* 2003; 82(10): 960-5.
[80] Sawaya GF, McConnell KJ, Kulasingam SL et al. Risk of cervical cancer associated with extending the interval between cervical-cancer screenings. *N Engl J Med.* 2003; 349(16): 1501-9.
[81] Wright TC, Jr., Cox JT, Massad LS et al. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *American Journal of Obstetrics & Gynecology.* 2003; 189(1): 295-304.
[82] Padilla-Paz LA, Carlson J, Twiggs LB et al. Evidence supporting the current management guidelines for high-grade squamous intraepithelial lesion cytology. *J Low Genit Tract Dis.* 2004; 8(2): 139-46.
[83] Peto J, Gilham C, Fletcher O et al. The cervical cancer epidemic that screening has prevented in the UK. *The Lancet.* 2004; 364(9430): 249-56.
[84] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.
[85] Taylor LA, Sorensen SV, Ray NF et al. Cost-effectiveness of the conventional papanicolaou test with a new adjunct to cytological screening for squamous cell carcinoma of the uterine cervix and its precursors. *Archives of Family Medicine.* 2000; 9(8): 713-21.
[86] Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstetrics & Gynecology.* 2003; 102(4): 765-73.

instance, increasing cervical cancer incidence is being reported in some European settings.[88,89]

Despite national programs aimed at detection, early intervention and follow-up monitoring,[90,91] cervical cancer still develops.[92] The standard therapy for carcinoma of the cervix is radiotherapy and surgery, used alone or together. Benedet at al. reviewed almost 14,000 cases from various countries: 45% were treated by radiotherapy alone, and a further 14% by radiotherapy in combination with surgery.[93] Chemotherapy was only rarely employed.

With treatment, the five-year survival rate seen in the same sample was about 70%. This compares well with data derived from the B.C. population (72%), as well as in the US (71%).[94] However, the survival rate varies greatly depending on the stage of cancer, as summarized in the following table.[95]

Stage	*Description of Cancer Development*	*Five year survival (%)*
I	Carcinoma strictly confined to the cervix.	78.8 – 98.7
II	Invasion beyond the uterus, but not to pelvic wall.	64.7 – 68.8
III	Extension to the pelvic wall; involvement of lower vagina.	40.4 – 43.3
IV	Beyond the pelvis or involvement of bladder or rectum.	15.0 – 19.5

Much is known about the complex interplay of viral DNA and host cellular mechanisms which leads to cervical cancer, generating many potentially useful biomarkers, as well as the possibility of gene and other molecular therapies.[96,97,98,99]

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[87] Smith HO, Tiffany MF, Qualls CR et al. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. *Gynecologic Oncology.* 2000; 78(2): 97-105.

[88] Bray F, Loos AH, McCarron P et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiology, Biomarkers & Prevention.* 2005; 14(3): 677-86.

[89] Dillner J. Trends over time in the incidence of cervical neoplasia in comparison to trends over time in human papillomavirus infection. *Journal of Clinical Virology.* 2000; 19(1-2): 7-23.

[90] Zielinski GD, Bais AG, Helmerhorst TJ et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. *Obstetrical & Gynecological Survey.* 2004; 59(7): 543-53.

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[92] Brinkmann D, Gladman MA, Norman S et al. Why do women still develop cancer of the cervix despite the existence of a national screening programme? *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2005; 119(1): 123-4.

[93] Benedet JL, Odicino F, Maisonneuve P et al. Carcinoma of the cervix uteri. *International Journal of Gynaecology & Obstetrics.* 2003; 83 Suppl 1: 41-78.

[94] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[95] Data from Benedet JL, Odicino F, Maisonneuve P et al. Carcinoma of the cervix uteri. *International Journal of Gynaecology & Obstetrics.* 2003; 83 Suppl 1: 41-78.

[96] Duggan MA. A review of the natural history of cervical intraepithelial neoplasia. *Gan to kagaku ryoho. Cancer & Chemotherapy.* 2002; 29 Suppl 1: 176-93.

[97] Anton M, Horky M, Blaha O. The role of tumour suppressors and viral oncoproteins in cervical carcinogenesis. *Ceská Gynekologie.* 2000; 65(4): 275-8.

Epidemiology

Cervical cancer has been the principal cancer of women in the *developing* world, though breast cancer may have overtaken it in the statistics; when the numbers from *developed* countries are added in, cervical cancer ends up ranking second or third among women globally, or about 10% of all female cancer cases.[100,101,102]

The estimated number of new cases of cervical cancer in Canada for 2005 is 1,350, while some 400 women are expected to die of the disease. The incidence rate in B.C., at about 7 per 100,000 women, represents about 150 new cases for 2005.[103] This actually reflects a decline in incidence compared with data from the 1990s.[104]

In Canada, incidence is particularly high within aboriginal populations; among the Inuit, cervical cancer accounts for 15% of female cancers, and the age-standardized rate among First Nations in Saskatchewan is 6 times higher than the national average.[105]

Apart from persistent infection with high-risk HPV types—and the consequent connection to sexual activity (see below)—proposed risk factors for progression of lesions towards cancer have included viral load, smoking, parity,[106] and long-term use of oral contraceptives.[107,108,109,110,111,112,113,114] In most cases, the associations are

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[98] Wolf JK, Franco EL, Arbeit JM et al. Innovations in understanding the biology of cervical cancer. *Cancer.* 2003; 98(9 Suppl): 2064-9.

[99] Wilson VG, Rosas-Acosta G. Molecular targets for papillomavirus therapy. *Current Drug Targets - Infectious Disorders.* 2003; 3(3): 221-39.

[100] Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine.* 2003; 348(6): 518-27.

[101] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[102] Schoell WM, Janicek MF, Mirhashemi R. Epidemiology and biology of cervical cancer. *Seminars in Surgical Oncology.* 1999; 16(3): 203-11.

[103] Canadian Cancer Society. *Canadian Cancer Statistics 2005.*

[104] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[105] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[106] Parity refers to the number of children ever born to a woman.

[107] Duggan MA. A review of the natural history of cervical intraepithelial neoplasia. *Gan to kagaku ryoho. Cancer & Chemotherapy.* 2002; 29 Suppl 1: 176-93.

[108] Kjellberg L, Hallmans G, Ahren AM et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *British Journal of Cancer.* 2000; 82(7): 1332-8.

[109] Wolf JK, Franco EL, Arbeit JM et al. Innovations in understanding the biology of cervical cancer. *Cancer.* 2003; 98(9 Suppl): 2064-9.

[110] Stanley MA. Human papillomavirus and cervical carcinogenesis. *Best Practice & Research Clinical Obstetrics and Gynaecology.* 2001; 15(5): 663-76.

[111] Plummer M, Herrero R, Franceschi S et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case--control study. *Cancer Causes Control.* 2003; 14(9): 805-14.

[112] Brinton LA, Schairer C, Haenszel W et al. Cigarette smoking and invasive cervical cancer. *Journal of the American Medical Association.* 1986; 255(23): 3265-9.

[113] Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *Journal of the National Cancer Institute Monograph.* 2003; (31): 20-8.

[114] Munoz N, Franceschi S, Bosetti C et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *The Lancet.* 2002; 359(9312): 1093-101.

still being studied and debated.[115,116,117] For example, "since smoking is associated with sexual behaviour, it is difficult to determine whether [the connection to cervical cancer] is spurious given the impossibility of effectively eliminating confounding through adjustment for measures of sexual activity."[118] The same qualification would have to be made concerning any association between cervical cancer and factors such as socioeconomic status and psychosocial stress.[119,120,121,122,123]

Nutritional factors such as beta carotene, folate and vitamins A and C appear to play a protective role.[124,125,126,127] Diet ultimately may influence between-country differences in cervical cancer rates, which could suggest a possible public health prevention strategy for regions with nutritional deficiency.[128,129]

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[115] Thomas DB, Ray RM, Qin Q. Risk factors for progression of squamous cell cervical carcinoma in-situ to invasive cervical cancer: results of a multinational study. *Cancer Causes Control.* 2002; 13(7): 683-90.

[116] Castellsague X, Bosch FX, Munoz N. Environmental co-factors in HPV carcinogenesis. *Virus Research.* 2002; 89(2): 191-9.

[117] Phillips AN, Smith GD. Cigarette smoking as a potential cause of cervical cancer: has confounding been controlled? *International Journal of Epidemiology.* 1994; 23(1): 42-9.

[118] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[119] Parikh S, Brennan P, Boffetta P. Meta-analysis of social inequality and the risk of cervical cancer. *International Journal of Cancer.* 2003; 105(5): 687-91.

[120] Newmann SJ, Garner EO. Social inequities along the cervical cancer continuum: a structured review. *Cancer Causes Control.* 2005; 16(1): 63-70.

[121] McFadden K, McConnell D, Salmond C et al. Socioeconomic deprivation and the incidence of cervical cancer in New Zealand: 1988-1998. *New Zealand Medical Journal.* 2004; 117(1206): U1172.

[122] Singh GK, Miller BA, Hankey BF et al. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival, 1975-2000. *Cancer.* 2004; 101(5): 1051-7.

[123] Coker AL, Bond S, Madeleine MM et al. Psychosocial stress and cervical neoplasia risk. *Psychosomatic Medicine.* 2003; 65(4): 644-51.

[124] Garcia-Closas R, Castellsague X, Bosch X et al. The role of diet and nutrition in cervical carcinogenesis: A review of recent evidence. *International Journal of Cancer.* 2005; Epublished ahead of print: May 23.

[125] Hernandez BY, McDuffie K, Wilkens LR et al. Diet and premalignant lesions of the cervix: evidence of a protective role for folate, riboflavin, thiamin, and vitamin B12. *Cancer Causes Control.* 2003; 14(9): 859-70.

[126] Giuliano AR, Siegel EM, Roe DJ et al. Dietary intake and risk of persistent human papillomavirus (HPV) infection: the Ludwig-McGill HPV Natural History Study. *Journal of Infectious Diseases.* 2003; 188(10): 1508-16.

[127] Potischman N, Brinton LA. Nutrition and cervical neoplasia. *Cancer Causes Control.* 1996; 7(1): 113-26.

[128] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.

[129] Shannon J, Thomas DB, Ray RM et al. Dietary risk factors for invasive and in-situ cervical carcinomas in Bangkok, Thailand. *Cancer Causes Control.* 2002; 13(8): 691-9.

Finally, co-infections may play a role in cervical carcinogenesis.[130,131,132,133] This is especially true with the immunocompromised conditions related to HIV. Infection with HIV has been shown to be a strong risk factor for precancerous lesions and at least *in-situ* cervical cancer.[134] In one study, 7% of about 400 HIV-positive women had HSILs, compared to 1% of 307 HIV-negative control subjects.[135] The evidence for a connection between HIV and *invasive* cervical cancer rates has been more equivocal.[136] Fortunately, the standard prevention programs are still effective for HIV-positive women, offering the possibility of reduced incidence of invasive cervical cancer.[137]

Relationship to HPV

One reviewer noted that "the understanding of cervical cancer as a preventable disease process hinges on the concept that it is fundamentally a sexually transmitted disease with a known causative agent: the human papillomavirus (HPV)."[138]

There is essentially a one-to-one connection between cervical cancer cases and the detection of HPV DNA, suggesting that "the prevention of HPV infection would virtually eliminate cervical cancer."[139] As Walboomers et al. concluded in 1999, "the presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer."[140] In short, HPV has been proposed as the first-ever necessary cause of a human cancer identified by researchers.[141,142] Put differently, there is a strong

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[130] Smith JS, Herrero R, Bosetti C et al. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *Journal of the National Cancer Institute.* 2002; 94(21): 1604-13.

[131] Smith JS, Munoz N, Herrero R et al. Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. *Journal of Infectious Diseases.* 2002; 185(3): 324-31.

[132] Koskela P, Anttila T, Bjorge T et al. Chlamydia trachomatis infection as a risk factor for invasive cervical cancer. *International Journal of Cancer.* 2000; 85(1): 35-9.

[133] Matsumoto K, Yasugi T, Oki A et al. Are smoking and chlamydial infection risk factors for CIN? Different results after adjustment for HPV DNA and antibodies. *British Journal of Cancer.* 2003; 89(5): 831-3.

[134] Ferenczy A, Coutlee F, Franco E et al. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. *Canadian Medical Association Journal.* 2003; 169(5): 431-4.

[135] Wright TC, Jr., Ellerbrock TV, Chiasson MA et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstetrics & Gynecology.* 1994; 84(4): 591-7.

[136] Chin KM, Sidhu JS, Janssen RS et al. Invasive cervical cancer in human immunodeficiency virus-infected and uninfected hospital patients. *Obstetrics & Gynecology.* 1998; 92(1): 83-7.

[137] Massad LS, Seaberg EC, Watts DH et al. Low incidence of invasive cervical cancer among HIV-infected US women in a prevention program. *AIDS.* 2004; 18(1): 109-13.

[138] Schoell WM, Janicek MF, Mirhashemi R. Epidemiology and biology of cervical cancer. *Seminars in Surgical Oncology.* 1999; 16(3): 203-11.

[139] Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. *Journal of the National Cancer Institute Monographs.* 2003; (31): 57-65.

[140] Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 1999; 189(1): 12-9.

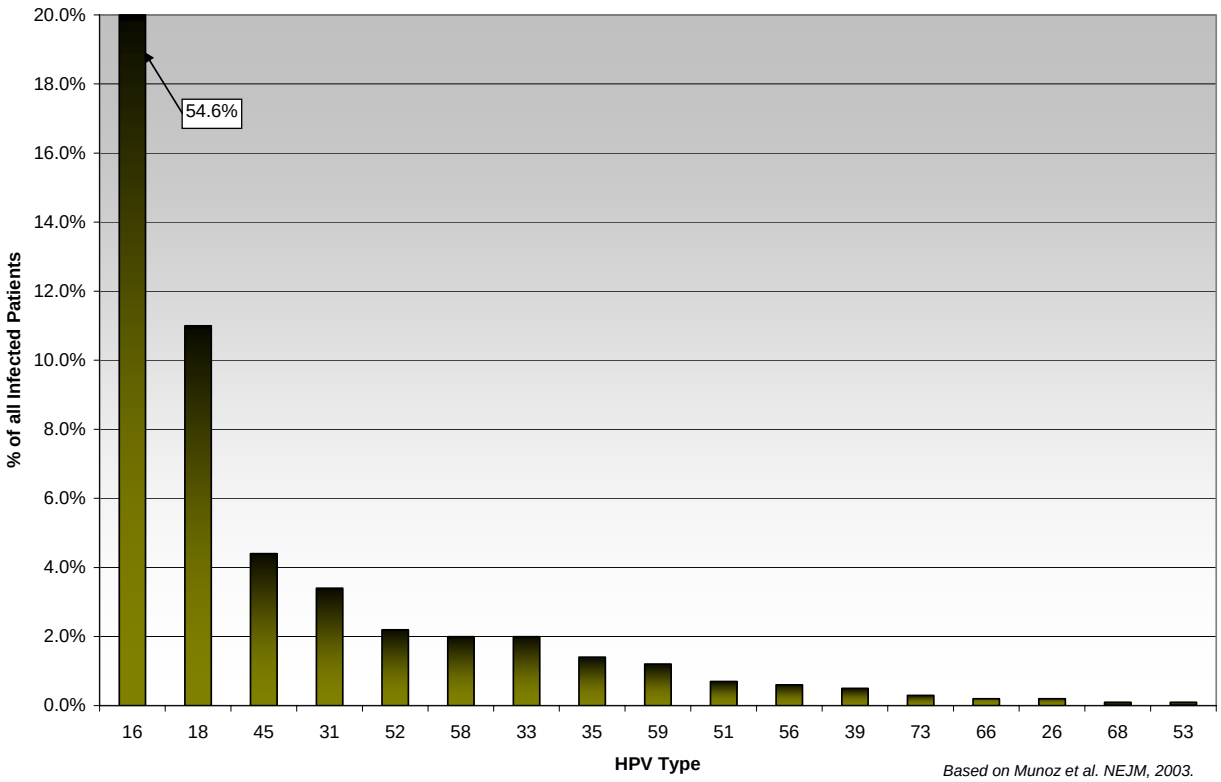
[141] Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus Research.* 2002; 89(2): 183-90.

[142] Bosch FX, Lorincz A, Munoz N et al. The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology.* 2002; 55(4): 244-65.

consensus implicating the persistence of "high risk" or oncogenic HPV types as the main risk factor for the development of cervical cancer.[143]

The high-risk HPV types are specifically identified in light of the risk of development of *cervical* cancer, as this disease dominates in the inventory of HPV-related cancers. Of the 30 HPV types spread through sexual contact and infecting the anogenital region, four are most often found within malignant cervical cells; HPV 16 accounts for about half the cases in the West, with types 18, 31, and 45 being associated with another 20 to 30% of cervical cancer cases (see the table below).[144,145] The other high-risk HPV types implicated in cervical cancer include 33, 35, 51, 52, 56, 58, 59 and another half dozen forms. There can be a differential association according to the histological type of precancerous lesion or cancer, e.g., HPV 18 is equally or even more prevalent than HPV 16 in cervical adenocarcinomas.[146] As will be seen in later sections, other HPV types preferentially promote other types of malignant and non-malignant disease in the human body, such as genital warts.

HPV Types and Cervical Cancer



[143] Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiologic Reviews.* 1988; 10: 122-63.
[144] Burd EM. Human papillomavirus and cervical cancer. *Clinical Microbiology Reviews.* 2003; 16(1): 1-17.
[145] Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine.* 2003; 348(6): 518-27.
[146] Andersson S, Rylander E, Larsson B et al. The role of human papillomavirus in cervical adenocarcinoma carcinogenesis. *European Journal of Cancer.* 2001; 37(2): 246-50.

As an expected corollary to the oncogenic significance of HPV, which is a sexually transmitted infection, there is a strong correlation between sexual activity and cervical cancer incidence. The important measures are number of sexual partners (lifetime and recent), age at first sexual intercourse, and sexual behaviour of the woman's male partners.[147] Unfortunately, strategies related to lifestyle interventions that might reduce the modifiable risk factors for cervical cancer have been slow to develop and be implemented.[148,149]

While HPV has been identified as a necessary cause of cervical cancer, the fact that a large percentage of women infected with high-risk HPV types do not progress to cancerous states demonstrates that the presence of the virus is usually not a *sufficient* cause of disease. Several potential co-agents have been noted above, including smoking and other infections. Genetic susceptibility in the host and genetic variants of the high-risk virus types have also been an area of intense interest in terms of explaining why only a subset of infected women develop cancer.[150,151] In particular, polymorphisms of the p53 gene have been investigated, but the results have been divergent.[152,153] Given the role of the immune system in controlling HPV infection, research has also focused on differences in the major histocompatability complex, a region of the host genome responsible for generating proteins known as human leucocyte antigen (HLA) class I and II antigens.[154,155]

The story becomes even more complex when the subtle variants within HPV types are factored in. For example, polymorphisms of the p53 gene seem to interact most significantly with certain variants of HPV 16 in terms of disease progression.[156,157] Of epidemiological interest is the fact that genotypes of HPV 16 seem to be related to geographical regions; European, Asian, American-Asian and African forms have

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[147] Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *Canadian Medical Association Journal.* 2001; 164(7): 1017-25.
[148] Benedet JL, Cabero-Roura L. Strategies for the modification of risk factors in gynecological cancers. *European Journal of Gynaecological Oncology.* 2002; 23(1): 5-10.
[149] Fernandez-Esquer ME, Ross MW, Torres I. The importance of psychosocial factors in the prevention of HPV infection and cervical cancer. *International Journal of STD & AIDS.* 2000; 11(11): 701-13.
[150] Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. *Virus Research.* 2002; 89(2): 229-40.
[151] Horng JT, Hu KC, Wu LC et al. Identifying the combination of genetic factors that determine susceptibility to cervical cancer. *IEEE Transactions on Information Technology in Biomedicine.* 2004; 8(1): 59-66.
[152] Andersson S, Rylander E, Strand A et al. The significance of p53 codon 72 polymorphism for the development of cervical adenocarcinomas. *British Journal of Cancer.* 2001; 85(8): 1153-6.
[153] de Araujo Souza PS, Villa LL. Genetic susceptibility to infection with human papillomavirus and development of cervical cancer in women in Brazil. *Mutation Research.* 2003; 544(2-3): 375-83.
[154] Zoodsma M, Nolte IM, Schipper M et al. Analysis of the entire HLA region in susceptibility for cervical cancer: a comprehensive study. *Journal of Medical Genetics.* 2005; 42(8): e49.
[155] Maciag PC, Schlecht NF, Souza PS et al. Major histocompatibility complex class II polymorphisms and risk of cervical cancer and human papillomavirus infection in Brazilian women. *Cancer Epidemiology, Biomarkers & Prevention.* 2000; 9(11): 1183-91.
[156] Zehbe I, Voglino G, Wilander E et al. p53 codon 72 polymorphism and various human papillomavirus 16 E6 genotypes are risk factors for cervical cancer development. *Cancer Research.* 2001; 61(2): 608-11.
[157] van Duin M, Snijders PJ, Vossen MT et al. Analysis of human papillomavirus type 16 E6 variants in relation to p53 codon 72 polymorphism genotypes in cervical carcinogenesis. *Journal of General Virology.* 2000; 81(Pt 2): 317-25.

been identified, with non-European viral types seeming to persist more frequently.[158] Even as such data accumulate, it must be acknowledged that the relationship between host polymorphisms and HPV variants remains "poorly understood."[159] Nonetheless, the promise is held out of one day routinely screening for genetic predisposing factors that may influence the likelihood of persistent HPV infection and the rate of tumour development.[160]

[158] Villa LL, Sichero L, Rahal P et al. Molecular variants of human papillomavirus types 16 and 18 preferentially associated with cervical neoplasia. *Journal of General Virology.* 2000; 81(Pt 12): 2959-68.
[159] Heilmann V, Kreienberg R. Molecular biology of cervical cancer and its precursors. *Current Women's Health Reports.* 2002; 2(1): 27-33.
[160] Magnusson PK, Lichtenstein P, Gyllensten UB. Heritability of cervical tumours. *International Journal of Cancer.* 2000; 88(5): 698-701.

Anogenital Cancers

Cancer of the Vulva

Description

The vulva is the skin and fatty tissue in women extending from the area of the anus to about an inch below the pubic hairline. Vulvar cancer mostly affects the two folds or labia (lips) around the vagina. The reported proportion of vulvar tumours that are squamous cell carcinomas varies from 75 to 90%.[161,162] Other forms of vulvar cancer include basal cell and verrucous carcinomas, as well as cancers of the Bartholin glands.[163] A stage IV carcinoma of the vulva, where the tumour has invaded well beyond the primary site to the upper urethra, bladder, pelvic bone, rectum and / or regional lymph nodes on both sides of the body, is the most serious.[164] In contrast, a stage I carconima is confined to the vulva and / or perineum.[165]

The standard treatment for vulvar cancer is surgery, augmented by radiation therapy in stages III and IV. Given the complications and psychosexual consequences of vulvectomy, there is a trend towards individualized management and, where possible, vulvar conservation.

As one might expect, survival rates steadily decrease as vulvar cancer spreads. However, for reasons that are not clear, there are widely varying reports of the rates associated with each clinical stage; the summary provided by the B.C. Cancer Agency is offered in the table below. [166]

Stage	*Five year survival rate*
I	80%
II	60
III	20-30
IV	<5

Epidemiology

Vulvar cancer is relatively uncommon, occurring at the rate of 2 per 100,000 women per year in industrialized countries, and accounting for only 3 to 5% of female genital tract malignancies.[167] This translates into the following U.S. figures:

Year	*Incidence*	*Mortality*
1998[168]	3,200	800
2005 (estimate)[169]	3,870	870

[161] Platz CE, Benda JA. Female genital tract cancer. *Cancer.* 1995; 75(1 Suppl): 270-94.
[162] Canavan TP, Cohen D. Vulvar cancer. *American Family Physician.* 2002; 66(7): 1269-74.
[163] The Bartholin glands are two glands located near the opening of the vagina in women. They secrete mucus to provide lubrication, especially when the woman is sexually aroused.
[164] Beller U, Maisonneuve P, Benedet JL et al. Carcinoma of the vulva. *International Journal of Gynaecology & Obstetrics.* 2003; 83 Suppl 1: 7-26.
[165] The short bridge of flesh between the anus and the vagina in women.
[166] Available at http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/Vulva/default.htm. Accessed August 2005.
[167] Canavan TP, Cohen D. Vulvar cancer. *American Family Physician.* 2002; 66(7): 1269-74.
[168] Landis SH, Murray T, Bolden S et al. Cancer statistics, 1998. *CA: A Cancer Journal for Clinicians.* 1998; 48(1): 6-29.
[169] American Cancer Society. *Cancer Facts and Figures 2005.*

Equivalent statistics for Canada could not be located, but estimates based on crude national population figures suggest an annual mortality of less than 100 women for the whole country.

Traditionally, vulvar cancer has been considered a disease of the elderly; indeed, the large majority of cases present at age 60 plus. By age 75, the incidence rate peaks at 20 per 100,000 women.[170] Recently, the incidence of both preinvasive and invasive vulvar carcinoma among younger women seems to have increased, which may reflect the prevalence of HPV in the female population.[171,172]

In addition to HPV infection per se (see below), studies have shown, not unexpectedly, that having multiple sexual partners and sexual initiation before age 19 years are risk factors for vulvar cancer.[173] Smoking also demonstrates a strong correlation with vulvar cancer development, though this is not necessarily a causal relationship.[174]

Relationship to HPV

Over the last decade it has been suggested that vulvar cancer is really two separate diseases.[175,176] One type involves non-neoplastic epithelial disorders which usually occurs in patients of advanced age, with a resulting poor prognosis.[177,178] The other type appears to involve HPV infection, which leads to vulvar intraepithelial neoplasia (VIN)[179] and a predisposition to full vulvar cancer.[180] Patients with HPV-positive

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[170] Crum CP. Carcinoma of the vulva: epidemiology and pathogenesis. *Obstetrics & Gynecology.* 1992; 79(3): 448-54.

[171] Joura EA, Losch A, Haider-Angeler MG et al. Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. *Journal of Reproductive Medicine.* 2000; 45(8): 613-5.

[172] Joura EA. Epidemiology, diagnosis and treatment of vulvar intraepithelial neoplasia. *Current Opinion in Obstetrics and Gynecology.* 2002; 14(1): 39-43.

[173] Basta A, Adamek K, Pitynski K. Intraepithelial neoplasia and early stage vulvar cancer. Epidemiological, clinical and virological observations. *European Journal of Gynaecology & Oncology.* 1999; 20(2): 111-4.

[174] Madeleine MM, Daling JR, Carter JJ et al. Cofactors with human papillomavirus in a population-based study of vulvar cancer. *Journal of the National Cancer Institute.* 1997; 89(20): 1516-23.

[175] Crum CP. Carcinoma of the vulva: epidemiology and pathogenesis. *Obstetrics & Gynecology.* 1992; 79(3): 448-54.

[176] Bonvicini F, Venturoli S, Ambretti S et al. Presence and type of oncogenic human papillomavirus in classic and in differentiated vulvar intraepithelial neoplasia and keratinizing vulvar squamous cell carcinoma. *Journal of Medical Virology.* 2005; 77(1): 102-6.

[177] Fox H, Wells M. Recent advances in the pathology of the vulva. *Histopathology.* 2003; 42(3): 209-16.

[178] Monk BJ, Burger RA, Lin F et al. Prognostic significance of human papillomavirus DNA in vulvar carcinoma. *Obstetrics & Gynecology.* 1995; 85(5 Pt 1): 709-15.

[179] A term invented in the 1980s for epithelial atypia and stage 0 or in-situ tumours, it has since been extended to include all morphologic changes believed to be potential precursors of invasive vulvar squamous cell carcinoma. The classification of vulvar squamous lesions remains a very complicated and fluid topic. See Hart WR. Vulvar intraepithelial neoplasia: historical aspects and current status. *International Journal of Gynecological Pathology.* 2001; 20(1): 16-30, Medeiros F, Nascimento AF, Crum CP. Early vulvar squamous neoplasia: advances in classification, diagnosis, and differential diagnosis. *Advances in Anatomic Pathology.* 2005; 12(1): 20-6.

[180] Only a small proportion of patients with a VIN 3 develop invasive vulvar cancer. One recent review of almost a hundred papers summarized the rate to be 6.5%. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecologic Oncology.* 2005; 97(2): 645-51.

carcinomas tend to be younger.[181] As one piece of supporting evidence for this theory of causation, a study of about 300 women with vulvar intraepithelial neoplasms or stage I vulvar carcinoma reported that 61.5% of younger women (under age 45 years) demonstrated an HPV infection, compared to only 17.5% of older women.[182] On another front, a 2005 study confirmed a high presence of HPV (66%) in classic vulvar intraepithelial neoplasms; perhaps more significantly, *all* of the patients that did *not* show classic neoplasms were HPV-negative.[183]

It should be noted that "the presence and role of various oncogenic types of HPV in vulvar intraepithelial neoplasia and in the promotion and development of vulvar carcinoma is still under discussion."[184] However, the evidence for such connections continues to grow, albeit through data which demonstrate great variation. Research results from the early 1990s across all ages showed that 31 to 57% of vulvar carcinomas demonstrated the presence of HPV infection.[185,186,187,188] When the cases of VIN are added to invasive vulvar carcinoma, the results are even more wide-ranging; in over a dozen papers between 1991 and 2005, from 20 to 90% of such patients were shown to be HPV-positive.[189,190,191] This variation is consistent with more recent data on HPV prevalence among vulvar cancer patients per se. Based on small samples, the figure reported by Ngan et al. (1999) was 48%, by Menczer et al.

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[181] Kagie MJ, Kenter GG, Zomerdijk-Nooijen Y et al. Human papillomavirus infection in squamous cell carcinoma of the vulva, in various synchronous epithelial changes and in normal vulvar skin. *Gynecologic Oncology.* 1997; 67(2): 178-83.

[182] Basta A, Adamek K, Pitynski K. Intraepithelial neoplasia and early stage vulvar cancer. Epidemiological, clinical and virological observations. *European Journal of Gynaecology & Oncology.* 1999; 20(2): 111-4.

[183] Bonvicini F, Venturoli S, Ambretti S et al. Presence and type of oncogenic human papillomavirus in classic and in differentiated vulvar intraepithelial neoplasia and keratinizing vulvar squamous cell carcinoma. *Journal of Medical Virology.* 2005; 77(1): 102-6.

[184] Bonvicini F, Venturoli S, Ambretti S et al. Presence and type of oncogenic human papillomavirus in classic and in differentiated vulvar intraepithelial neoplasia and keratinizing vulvar squamous cell carcinoma. *Journal of Medical Virology.* 2005; 77(1): 102-6.

[185] Ansink AC, Krul MR, De Weger RA et al. Human papillomavirus, lichen sclerosus, and squamous cell carcinoma of the vulva: detection and prognostic significance. *Gynecologic Oncology.* 1994; 52(2): 180-4.

[186] Lee YY, Wilczynski SP, Chumakov A et al. Carcinoma of the vulva: HPV and p53 mutations. *Oncogene.* 1994; 9(6): 1655-9.

[187] Bloss JD, Liao SY, Wilczynski SP et al. Clinical and histologic features of vulvar carcinomas analyzed for human papillomavirus status: evidence that squamous cell carcinoma of the vulva has more than one etiology. *Human Pathology.* 1991; 22(7): 711-8.

[188] Toki T, Kurman RJ, Park JS et al. Probable nonpapillomavirus etiology of squamous cell carcinoma of the vulva in older women: a clinicopathologic study using in situ hybridization and polymerase chain reaction. *International Journal of Gynecological Pathology.* 1991; 10(2): 107-25.

[189] Bonvicini F, Venturoli S, Ambretti S et al. Presence and type of oncogenic human papillomavirus in classic and in differentiated vulvar intraepithelial neoplasia and keratinizing vulvar squamous cell carcinoma. *Journal of Medical Virology.* 2005; 77(1): 102-6. The authors summarize results from a number of papers.

[190] Kim YT, Thomas NF, Kessis TD et al. p53 mutations and clonality in vulvar carcinomas and squamous hyperplasias: evidence suggesting that squamous hyperplasias do not serve as direct precursors of human papillomavirus-negative vulvar carcinomas. *Human Pathology.* 1996; 27(4): 389-95.

[191] Almeida G, do Val I, Gondim C et al. Human papillomavirus, Epstein-Barr virus and p53 mutation in vulvar intraepithelial neoplasia. *Journal of Reproductive Medicine.* 2004; 49(10): 796-9.

(2000) 64%, and by Koyamatsu et al. (2003) only 13%.[192,193,194] One 2005 study, also drawing on a small cohort, showed a significantly higher rate of HPV detection in vulvar tumours (75%).[195]

A 2003 study offered a clear breakdown of the HPV relationship to different vulvar pathologies:[196]

Presentation	*HPV positivity*
Intraepithelial neoplasm, grade 3	57.9%
Superficially invasive carcinoma	33.3
Invasive squamous cell carcinoma	7.3

This table suggests that much of the variation in the observed relationship between HPV and vulvar cancer may arise out of different definitions of what represents "true" cancer; the small samples also might play a role in generating heterogeneous data.

In the study by Ngan and colleagues noted above, HPV 16 and 18 accounted for 96% of the cases of infection; Menczer and co-workers, with their 64% HPV positivity, in fact only looked for these two viral types. Their results should be compared with an earlier study which zeroed in on one viral type, ultimately detecting HPV 16 in 83% of the infected cancer patients.[197] The domination of HPV 16 in vulvar cancer was confirmed in 2004 by Almeida et al., as well as in 2005 by Bonvicini et al. (who detected this viral type in 81.8% of the classic cases of VIN).[198,199] Another study

[192] Ngan HY, Cheung AN, Liu SS et al. Abnormal expression or mutation of TP53 and HPV in vulvar cancer. *European Journal of Cancer.* 1999; 35(3): 481-4.
[193] Menczer J, Fintsi Y, Arbel-Alon S et al. The presence of HPV 16, 18 and p53 immunohistochemical staining in tumor tissue of Israeli Jewish women with cervical and vulvar neoplasia. *European Journal of Gynaecological Oncology.* 2000; 21(1): 30-4.
[194] Koyamatsu Y, Yokoyama M, Nakao Y et al. A comparative analysis of human papillomavirus types 16 and 18 and expression of p53 gene and Ki-67 in cervical, vaginal, and vulvar carcinomas. *Gynecologic Oncology.* 2003; 90(3): 547-51.
[195] Huang FY, Kwok YK, Lau ET et al. Genetic abnormalities and HPV status in cervical and vulvar squamous cell carcinomas. *Cancer Genetics & Cytogenetics.* 2005; 157(1): 42-8. For an even higher rate of HPV positivity in both VIN and VSCC, see Ueda Y, Enomoto T, Miyatake T et al. Analysis of clonality and HPV infection in benign, hyperplastic, premalignant, and malignant lesions of the vulvar mucosa. *American Journal of Clinical Pathology.* 2004; 122(2): 266-74.
[196] Engelman DE, Andrade LA, Vassallo J. Human papillomavirus infection and p53 protein expression in vulvar intraepithelial neoplasia and invasive squamous cell carcinoma. *Brazilian Journal of Medical & Biological Research.* 2003; 36(9): 1159-65.
[197] Kagie MJ, Kenter GG, Tollenaar RA et al. p53 protein overexpression is common and independent of human papillomavirus infection in squamous cell carcinoma of the vulva. *Cancer.* 1997; 80(7): 1228-33.
[198] Almeida G, do Val I, Gondim C et al. Human papillomavirus, Epstein-Barr virus and p53 mutation in vulvar intraepithelial neoplasia. *Journal of Reproductive Medicine.* 2004; 49(10): 796-9.
[199] Bonvicini F, Venturoli S, Ambretti S et al. Presence and type of oncogenic human papillomavirus in classic and in differentiated vulvar intraepithelial neoplasia and keratinizing vulvar squamous cell carcinoma. *Journal of Medical Virology.* 2005; 77(1): 102-6.

established an even higher rate of HPV 16 positivity among 58 cases of VIN 3 or vulvar squamous cell carcinoma, namely 90%.[200]

In sum, the involvement of HPV in the etiology of vulvar cancer is becoming almost as well established has it has been for cervical carcinogenesis.

Cancer of the Vagina

Description

The vagina extends from the vulva upward to the uterine cervix. Vaginal neoplasia are uncommon; in fact, primary vaginal cancers appear to be one of the rarest malignancies in the body.[201] When cancer is detected, it is often associated with cervical or vulvar cancers, so these diseases must be excluded before a primary vaginal cancer can be confirmed.

The most common tissue affected in vaginal cancer is the squamous epithelium; in a large sample derived from the US National Cancer Data Base, 79% of the cases were this type, and a further 14% were adenocarcinomas.[202] The small proportion of other cancers of the vagina reported in the literature include melanomas, mucosa-associated lymphoid tissue lymphomas, angiomyxomas, rhabdomyosarcomas, angiofibroblastomas, and adenosarcomas, all of which are exceedingly rare.[203,204,205,206,207,208,209] Malignant melanomas, for instance, represent less than 1% of all vaginal cancers.[210]

The lesions associated with precancerous vaginal intraepithelial neoplasia (VAIN) and full cancer are most commonly found in the upper third of the vagina (i.e., nearest the cervix). VAIN is highly curable through local excision or ablative therapy, but the close proximity of the rectum, bladder and urethra makes treatment of actual malignancies more difficult.[211,212] Recommended therapy varies with disease stage. Surgery is most common with in-situ (stage 0) carcinomas, while

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201 Creasman WT, Phillips JL, Menck HR. The National Cancer Data Base report on cancer of the vagina. *Cancer.* 1998; 83(5): 1033-40.

202 Creasman WT, Phillips JL, Menck HR. The National Cancer Data Base report on cancer of the vagina. *Cancer.* 1998; 83(5): 1033-40.

203 Moodley M, Daya M, Moodley J. Vaginal malignant melanoma: a case report and literature review. *International Journal of Gynecological Cancer.* 2004; 14(4): 687-9.

204 Miner TJ, Delgado R, Zeisler J et al. Primary vaginal melanoma: a critical analysis of therapy. *Annals of Surgical Oncology.* 2004; 11(1): 34-9.

205 Yoshinaga K, Akahira J, Niikura H et al. A case of primary mucosa-associated lymphoid tissue lymphoma of the vagina. *Human Pathology.* 2004; 35(9): 1164-6.

206 Papachristou DJ, Batistatou A, Paraskevaidis E et al. Aggressive angiomyxoma of the vagina: a case report and review of the literature. *European Journal of Gynaecologic Oncology.* 2004; 25(4): 519-21.

207 Suzuki Y, Sakurai H, Hasegawa M et al. A case of rhabdomyosarcoma of the vagina in an elderly woman. *European Journal of Gynaecological Oncology.* 2004; 25(4): 509-11.

208 McCluggage WG, White RG. Angiomyofibroblastoma of the vagina. *Journal of Clinical Pathology.* 2000; 53(10): 803.

209 Toyoshima M, Akahira J, Moriya T et al. Primary vaginal adenosarcoma with sarcomatous overgrowth. *Gynecologic Oncology.* 2004; 95(3): 759-61.

210 Creasman WT. Vaginal cancers. *Current Opinion in Obstetrics & Gynecology.* 2005; 17(1): 71-6.

211 Creasman WT. Vaginal cancers. *Current Opinion in Obstetrics & Gynecology.* 2005; 17(1): 71-6.

212 Cardosi RJ, Bomalaski JJ, Hoffman MS. Diagnosis and management of vulvar and vaginal intraepithelial neoplasia. *Obstetrics & Gynecology Clinics of North America.* 2001; 28(4): 685-702.

radiation is used more often in the higher stages. Chemotherapy is used in a quarter of stage III and IV cases. Surgery dominates in melanoma treatment, as many physicians do not believe radiation is effective with this highly malignant disease.[213] As for the various sarcomas, chemotherapy is both common and effective, especially in paediatric cases; with older patients, surgery and radiation therapy again begin to emerge as the key options.

While melanomas have a poor prognosis (14% survival at 5 years), the situation with epithelial cancers is better. The reported 5 year survival rate for stage I carcinomas is 64 to 90%, dropping to 0 to 40% at the higher stages.[214]

Epidemiology

Vaginal cancers represent only 0.5 to 3% of all female genital tract cancers.[215,216,217] They are much rarer than carcinomas of the cervix or vulva. The global incidence rate is less than 1 per 100,000 women. Nova Scotia is the province with the highest rate, namely, 0.8 per 100,000, which actually is fourth highest in the world.[218] There is evidence that the frequency of VAIN is increasing, especially among younger women.[219]

A recent population-based study identified lifetime number of sexual partners, early age at first intercourse, and smoking were associated with an increased risk of in situ and invasive vaginal cancer. There is also evidence of genetic susceptibility.[220]

Relationship to HPV

A study in 1997 found an 83% HPV positivity rate over 71 cases of VAIN. Over 20 types of HPV were detected.[221] A more recent study with double the number of cases confirmed these results, with 82.4% positivity in the in situ cancers and 64% positivity in invasive cancers, comprising a variety of HPV types; however, HPV 16 dominated, detected in over half the in situ and invasive cases.[222] This was consistent with a 2003 study, which found HPV 16 or 18 DNA in 44% of cancers in a small number of vaginal cancer cases.[223]

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[213] Creasman WT, Phillips JL, Menck HR. The National Cancer Data Base report on cancer of the vagina. *Cancer.* 1998; 83(5): 1033-40.
[214] Duarte-Franco E, Franco EL. Other Gynecologic Cancers: endometrial, ovarian, vulvar and vaginal cancers. *BMC Womens Health.* 2004; 4 Suppl 1: S14.
[215] Creasman WT. Vaginal cancers. *Current Opinion in Obstetrics & Gynecology.* 2005; 17(1): 71-6.
[216] Beller U, Maisonneuve P, Benedet JL et al. Carcinoma of the vagina. *International Journal of Gynaecology & Obstetrics.* 2003; 83 Suppl 1: 27-39.
[217] Cardosi RJ, Bomalaski JJ, Hoffman MS. Diagnosis and management of vulvar and vaginal intraepithelial neoplasia. *Obstetrics & Gynecology Clinics of North America.* 2001; 28(4): 685-702.
[218] Duarte-Franco E, Franco EL. Other Gynecologic Cancers: endometrial, ovarian, vulvar and vaginal cancers. *BMC Womens Health.* 2004; 4 Suppl 1: S14.
[219] Cardosi RJ, Bomalaski JJ, Hoffman MS. Diagnosis and management of vulvar and vaginal intraepithelial neoplasia. *Obstetrics & Gynecology Clinics of North America.* 2001; 28(4): 685-702.
[220] Duarte-Franco E, Franco EL. Other Gynecologic Cancers: endometrial, ovarian, vulvar and vaginal cancers. *BMC Womens Health.* 2004; 4 Suppl 1: S14.
[221] Sugase M, Matsukura T. Distinct manifestations of human papillomaviruses in the vagina. *International Journal of Cancer.* 1997; 72(3): 412-5.
[222] Daling JR, Madeleine MM, Schwartz SM et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. *Gynecologic Oncology.* 2002; 84(2): 263-70.
[223] Koyamatsu Y, Yokoyama M, Nakao Y et al. A comparative analysis of human papillomavirus types 16 and 18 and expression of p53 gene and Ki-67 in cervical, vaginal, and vulvar carcinomas. *Gynecologic Oncology.* 2003; 90(3): 547-51.

The conclusion is that HPV DNA is found in the majority of vaginal tumours, and thus is clearly implicated in the etiology of this type of cancer.

Cancer of the Penis

Description

Most anogenital HPV infections in men cause no signs or symptoms. The most common public health consequence is transmission to female partners, and the most frequent clinical manifestation is genital warts (see section below).[224] The HPV-related male genital cancers include the penile and scrotal types; neither testicular nor prostate cancer has been linked to HPV infection.

Scrotal cancers are exceedingly rare; one study of 1.1 million men in Finland observed only 6 cases over a 25 year period.[225] Malignancies of the penis are more frequent but still relatively uncommon in developed settings, though in some developing countries they may account for 10 to 20% of male cancers.[226,227]

Of all cancers affecting the penis, 95% are squamous cell carcinomas.[228] Basaloid, verrucous, sarcomatoid and condylomatous (warty) variants occur only very rarely.[229,230,231,232] Cases of sarcoma, melanoma, basal cell carcinoma[233] and other histological presentations are likewise observed very infrequently;[234] melanomas, for instance, account for only about 1.4% of all primary penile carcinomas.[235]

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[224] Dunne EF, Burstein GR, Stone KM. Anogenital human papillomavirus infection in males. *Adolescent Medicine.* 2003; 14(3): 613-32, vi-vii.

[225] Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971-95. *International Journal of Cancer.* 2002; 102(6): 643-8.

[226] Pow-Sang MR, Benavente V, Pow-Sang JE et al. Cancer of the penis. *Cancer Control.* 2002; 9(4): 305-14.

[227] Burgers JK, Badalament RA, Drago JR. Penile cancer. Clinical presentation, diagnosis, and staging. *Urologic Clinics of North America.* 1992; 19(2): 247-56.

[228] Micali G, Innocenzi D, Nasca MR et al. Squamous cell carcinoma of the penis. *Journal of the American Academy of Dermatology.* 1996; 35(3 Pt 1): 432-51.

[229] Cubilla AL, Reuter VE, Gregoire L et al. Basaloid squamous cell carcinoma: a distinctive human papilloma virus-related penile neoplasm: a report of 20 cases. *American Journal of Surgical Pathology.* 1998; 22(6): 755-61.

[230] Seixas AL, Ornellas AA, Marota A et al. Verrucous carcinoma of the penis: retrospective analysis of 32 cases. *Journal of Urology.* 1994; 152(5 Pt 1): 1476-8; discussion 8-9.

[231] Lont AP, Gallee MP, Snijders P et al. Sarcomatoid squamous cell carcinoma of the penis: a clinical and pathological study of 5 cases. *Journal of Urology.* 2004; 172(3): 932-5.

[232] Cubilla AL, Velazques EF, Reuter VE et al. Warty (condylomatous) squamous cell carcinoma of the penis: a report of 11 cases and proposed classification of 'verruciform' penile tumors. *American Journal of Surgery & Pathology.* 2000; 24(4): 505-12.

[233] Ribuffo D, Alfano C, Ferrazzoli PS et al. Basal cell carcinoma of the penis and scrotum with cutaneous metastases. *Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery.* 2002; 36(3): 180-2.

[234] Pow-Sang MR, Benavente V, Pow-Sang JE et al. Cancer of the penis. *Cancer Control.* 2002; 9(4): 305-14.

[235] Sanchez-Ortiz R, Huang SF, Tamboli P et al. Melanoma of the penis, scrotum and male urethra: a 40-year single institution experience. *Journal of Urology.* 2005; 173(6): 1958-65.

A complex variety of HPV-related tumours can occur on male genitals.[236,237] For example, a nonmalignant lesion, bowenoid papulosis, is common in young sexually active adults.[238] Bowen's disease (or simply Bowen's) is a general term used by dermatologists for squamous cell carcinoma in situ (though some people restrict the term to premalignant neoplasia). Bowen's of the penis, erythroplasia of Queyrat (a special name for Bowen's of the glans penis), and bowenoid papulosis may be confused with a variety of other lesions on the penis. While all appear histologically as carcinoma in situ, and are strongly associated with HPV infection, only Bowen's disease and erythroplasia of Queyrat have been demonstrated to lead to invasive squamous cell carcinoma.[239] In contrast, bowenoid papulosis has a benign course with little evidence suggesting the potential for malignant development.[240,241]

The stages of penile cancer development are described in the following table.[242]

Stage	*Clinical description*
0	In situ, affects only the surface layer.
I	Invades subepithelial connective tissue.
II	Invades corpus spongiosum or cavernosum.
III	Invades urethra or prostate.
IV	Invades other adjacent structures.

Given the small number of patients, the best management of penile squamous cell carcinoma is difficult to research;[243] depending on cancer staging, treatment can comprise various types of surgery, including micrographic and laser, as well as radiotherapy and chemotherapy.[244,245] Multimodal approaches may be the best avenue when treating advanced cancer.[246] While vigorous approaches to treating penile intraepithelial neoplasia are recommended,[247] conservative therapies have been increasingly examined for premaligant or in situ stages and to prevent recurrence of cancer—with the obvious goal of preserving the penis where possible.[248,249,250,251] For

[236] Cubilla AL, Meijer CJ, Young RH. Morphological features of epithelial abnormalities and precancerous lesions of the penis. *Scandinavian Journal of Urology & Nephrology.* 2000; (205): 215-9.
[237] Bunker CB. Topics in penile dermatology. *Clinical & Experimental Dermatology.* 2001; 26(6): 469-79.
[238] Buechner SA. Common skin disorders of the penis. *BJU International.* 2002; 90(5): 498-506.
[239] Micali G, Innocenzi D, Nasca MR et al. Squamous cell carcinoma of the penis. *Journal of the American Academy of Dermatology.* 1996; 35(3 Pt 1): 432-51.
[240] Gerber GS. Carcinoma in situ of the penis. *Journal of Urology.* 1994; 151(4): 829-33.
[241] Dunne EF, Burstein GR, Stone KM. Anogenital human papillomavirus infection in males. *Adolescent Medicine.* 2003; 14(3): 613-32, vi-vii.
[242] Adapted from the B.C. Cancer Agency website at http://www.bccancer.bc.ca/PPI/TypesofCancer/Penis/default.htm. Accessed August 2005.
[243] Singh R, James ND, Watkin NA. Future development of penile cancer services in the UK. *BJU International.* 2004; 94(7): 967-9.
[244] Buechner SA. Common skin disorders of the penis. *BJU International.* 2002; 90(5): 498-506.
[245] Gerber GS. Carcinoma in situ of the penis. *Journal of Urology.* 1994; 151(4): 829-33.
[246] Culkin DJ, Beer TM. Advanced penile carcinoma. *Journal of Urology.* 2003; 170(2 Pt 1): 359-65.
[247] Porter WM, Francis N, Hawkins D et al. Penile intraepithelial neoplasia: clinical spectrum and treatment of 35 cases. *British Journal of Dermatology.* 2002; 147(6): 1159-65.
[248] Sanchez-Ortiz RF, Pettaway CA. Natural history, management, and surveillance of recurrent squamous cell penile carcinoma: a risk-based approach. *Urologic Clinics of North America.* 2003; 30(4): 853-67.
[249] Micali G, Nasca MR, Innocenzi D et al. Invasive penile carcinoma: a review. *Dermatologic Surgery.* 2004; 30(2 Pt 2): 311-20.

example, the topical immunomodulatory agent known as imiquimod has been shown to be effective in the management of Bowen's disease.[252,253] Importantly, urination and sexual function can often be maintained even when a significant portion of the penis must be removed (i.e., a partial penectomy).

The outcome can be good with early diagnosis and treatment. At the same time, one study observed recurrence and disease progression after therapy in up to 43% of stage I cases, suggesting the importance of follow-up surveillance and therapy.[254] The 5-year survival rate for penile cancers has been reported as 52 to 65%,[255] though at least one study showed a rate closer to 70% at 10 years.[256] The B.C. Cancer Agency reports a 5-year survival of 85 to 90%, dropping to as low as 30% if cancer has spread to the lymph nodes in the groin.[257] When such metastases do occur, lymphadenectomy has been shown to be effective;[258] some studies show that elective groin dissection is indicated in all but the mildest cases of penile cancer, but this remains extremely controversial.[259,260,261]

Epidemiology

As noted above, cancer of the penis is relatively rare, with an age-standardized global incidence rate of 0.3 to 1.0 per 100,000 men according to one report.[262] This compares with a result of 1.3 per 100,000 for cancers reported in England in 1998; by contrast, the incidence rate of prostate cancer was 60 times higher.[263] In the US, the incidence is about 1.5 per 100,000, equating to about 0.4 to 0.6% of all male cancers

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[250] Mobilio G, Ficarra V. Genital treatment of penile carcinoma. *Current Opinion in Urology.* 2001; 11(3): 299-304.

[251] Busby JE, Pettaway CA. What's new in the management of penile cancer? *Current Opinion in Urology.* 2005; 15(5): 350-7.

[252] Arlette JP. Treatment of Bowen's disease and erythroplasia of Queyrat. *British Journal of Dermatology.* 2003; 149 Suppl 66: 43-9.

[253] Kaspari M, Gutzmer R, Kiehl P et al. Imiquimod 5% cream in the treatment of human papillomavirus-16-positive erythroplasia of Queyrat. *Dermatology.* 2002; 205(1): 67-9.

[254] Munro NP, Thomas PJ, Deutsch GP et al. Penile cancer: a case for guidelines. *Annals of the Royal College of Surgeons of England.* 2001; 83(3): 180-5.

[255] Solsona E, Algaba F, Horenblas S et al. EAU Guidelines on Penile Cancer. *European Urology.* 2004; 46(1): 1-8.

[256] Bezerra AL, Lopes A, Santiago GH et al. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer.* 2001; 91(12): 2315-21.

[257] Available at at http://www.bccancer.bc.ca/PPI/TypesofCancer/Penis/default.htm. Accessed August 2005. Others have reported a worse prognosis once pelvic lymph nodes are involved, as little as 5% survival at 5 years. Culkin DJ, Beer TM. Advanced penile carcinoma. *Journal of Urology.* 2003; 170(2 Pt 1): 359-65.

[258] Stancik I, Holtl W. Penile cancer: review of the recent literature. *Current Opinion in Urology.* 2003; 13(6): 467-72.

[259] Chen MF, Chen WC, Wu CT et al. Contemporary management of penile cancer including surgery and adjuvant radiotherapy: an experience in Taiwan. *World Journal of Urology.* 2004; 22(1): 60-6.

[260] Mobilio G, Ficarra V. Genital treatment of penile carcinoma. *Current Opinion in Urology.* 2001; 11(3): 299-304.

[261] Singh I, Khaitan A. Current trends in the management of carcinoma penis--a review. *International Urology and Nephrology.* 2003; 35(2): 215-25.

[262] Buechner SA. Common skin disorders of the penis. *BJU International.* 2002; 90(5): 498-506.

[263] Office for National Statistics. Cancer registration statistics. 1998. Available at http://www.statistics.gov.uk/downloads/theme_health/MB1_No29/MB1_No29.pdf. Accessed August 2005.

and only 2% of cancer cases related to the genitals.[264,265] As suggested earlier, this type of cancer is a greater problem in developing countries; in Brazil, for example, the age-adjusted incidence rate is 8.3 per 100,000, accounting for 6% of male cancers.[266] The local context precisely follows the pattern expected for developed settings; a total of approximately 30 new cases of penile cancer were reported in B.C. in 2003.

While the incidence of penile cancer was reported to be stable or slightly increasing throughout Europe in the last two decades,[267] there is evidence that the incidence is actually declining in some countries.[268]

The age of peak incidence for penile cancer has been variously reported, either between 40 and 50 years or 70 years plus.[269,270]

The risk factors for penile cancer include high levels of sexual activity (30+ partners), penile trauma, conditions inducing chronic inflammation, and smoking.[271,272] Co-infections (other than with HPV), immunosuppression and ultraviolet radiation (used in the treatment of psoriasis) may also play a role in carcinogenesis.[273,274] There have been conflicting reports concerning an association both with cervical cancer in sexual partners and with herpes infections.[275]

The lack of neonatal circumcision is consistently revealed to be the strongest risk factor for cancer of the penis, though the implications remain controversial among some authorities.[276,277] A 1996 review noted that of the approximately 50,000 cases of

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[264] Rippentrop JM, Joslyn SA, Konety BR. Squamous cell carcinoma of the penis: evaluation of data from the surveillance, epidemiology, and end results program. *Cancer.* 2004; 101(6): 1357-63.
[265] Micali G, Innocenzi D, Nasca MR et al. Squamous cell carcinoma of the penis. *Journal of the American Academy of Dermatology.* 1996; 35(3 Pt 1): 432-51.
[266] Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. *Lancet Oncology.* 2004; 5(4): 240-7.
[267] Mosconi AM, Roila F, Gatta G et al. Cancer of the penis. *Critical Reviews in Oncology/Hematology.* 2005; 53(2): 165-77.
[268] Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971-95. *International Journal of Cancer.* 2002; 102(6): 643-8.
[269] Micali G, Innocenzi D, Nasca MR et al. Squamous cell carcinoma of the penis. *Journal of the American Academy of Dermatology.* 1996; 35(3 Pt 1): 432-51.
[270] Mosconi AM, Roila F, Gatta G et al. Cancer of the penis. *Critical Reviews in Oncology/Hematology.* 2005; 53(2): 165-77.
[271] Maden C, Sherman KJ, Beckmann AM et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *Journal of the National Cancer Institite.* 1993; 85(1): 19-24.
[272] Dillner J, von Krogh G, Horenblas S et al. Etiology of squamous cell carcinoma of the penis. *Scandinavian Journal of Urology and Nephrology.* 2000; (205): 189-93.
[273] Tseng HF, Morgenstern H, Mack T et al. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes & Control.* 2001; 12(3): 267-77.
[274] Aubin F, Puzenat E, Arveux P et al. Genital squamous cell carcinoma in men treated by photochemotherapy. A cancer registry-based study from 1978 to 1998. *British Journal of Dermatology.* 2001; 144(6): 1204-6.
[275] Mosconi AM, Roila F, Gatta G et al. Cancer of the penis. *Critical Reviews in Oncology/Hematology.* 2005; 53(2): 165-77.
[276] Schoen EJ, Wiswell TE, Moses S. New policy on circumcision--cause for concern. *Pediatrics.* 2000; 105(3 Pt 1): 620-3.

penile cancer in the US over the preceding 55 years, only 11 involved men who were circumcised as newborns.[278] A review by Moses et al. concluded that neonatal circumcision reduced the risk of penile cancer by at least 10-fold.[279] A controlled study in 1993 offered less dramatic but still compelling results: the risk of penile cancer was 3.2 times greater among men who had never been circumcised.[280] Despite this data, many are reluctant to classify or promote circumcision as a preventive measure; instead, they focus attention on other possibly modifiable factors such as sexual hygiene and phimosis (an abnormal constriction or tightness of the foreskin preventing retraction over the glans). Circumstantial evidence for shifting the focus somewhat off circumcision has emerged in countries like Denmark, which has both a very low circumcision rate (about 1.6%) and a declining incidence of penile cancer.[281]

Relationship to HPV

While not as well studied as it is in the context of female genital neoplasia and cancers, HPV DNA is consistently detected in lesions and cancers of the male genitals.[282,283] Nonetheless, though the evidence continues to build, an etiological connection between HPV and penile cancer is not yet considered to be fully established.[284,285] Interestingly, it has recently been demonstrated that male circumcision is associated with a reduced risk of penile HPV infection, thus linking these traditional and more contemporary risk factors for cancer of the penis.[286]

Earlier reports have suggested that HPV DNA is present in 75 to 100% of penile intraepithelial neoplasia (PIN).[287,288] This result, which has been confirmed in recent studies, would be more compelling, were it not for the fact that PIN is only a clear precursor for the small percentage of carcinomas of the basaloid or warty subtype; it is consistent that these variants also demonstrate the highest prevalence for HPV (47

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[277] Bunker CB. Topics in penile dermatology. *Clinical & Experimental Dermatology.* 2001; 26(6): 469-79.

[278] Micali G, Innocenzi D, Nasca MR et al. Squamous cell carcinoma of the penis. *Journal of the American Academy of Dermatology.* 1996; 35(3 Pt 1): 432-51.

[279] Moses S, Bailey RC, Ronald AR. Male circumcision: assessment of health benefits and risks. *Sexually Transmitted Infections.* 1998; 74(5): 368-73.

[280] Maden C, Sherman KJ, Beckmann AM et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *Journal of the National Cancer Institite.* 1993; 85(1): 19-24.

[281] Frisch M, Friis S, Kjaer SK et al. Falling incidence of penis cancer in an uncircumcised population (Denmark 1943-90). *British Medical Journal.* 1995; 311(7018): 1471.

[282] Dianzani C, Calvieri S, Pierangeli A et al. Identification of human papilloma viruses in male dysplastic genital lesions. *New Microbiologica.* 2004; 27(1): 65-9.

[283] Daling JR, Madeleine MM, Johnson LG et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *International Journal of Cancer.* 2005; 116(4): 606-16.

[284] Mosconi AM, Roila F, Gatta G et al. Cancer of the penis. *Critical Reviews in Oncology/Hematology.* 2005; 53(2): 165-77.

[285] Culkin DJ, Beer TM. Advanced penile carcinoma. *Journal of Urology.* 2003; 170(2 Pt 1): 359-65.

[286] Castellsague X, Bosch FX, Munoz N et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *New England Journal of Medicine.* 2002; 346(15): 1105-12.

[287] Aynaud O, Ionesco M, Barrasso R. Penile intraepithelial neoplasia. Specific clinical features correlate with histologic and virologic findings. *Cancer.* 1994; 74(6): 1762-7.

[288] Dillner J, von Krogh G, Horenblas S et al. Etiology of squamous cell carcinoma of the penis. *Scandinavian Journal of Urology and Nephrology.* 2000; (205): 189-93.

to 80% for basaloid and 75 to 100% for warty).[289,290] By contrast, the precursor lesion and development pathway for the dominant type of carcinoma, i.e., squamous cell, are not well understood;[291] furthermore, this type only demonstrated the presence of HPV DNA in about 35% of cases in one study, though more recent research has elevated the estimate.[292] Against this backdrop of possibly independent pathways of cancer development (similar to the story for vulvar cancer—see above), the overall HPV prevalence in penile carcinoma worked out to about 42%.[293] A 2005 study with a similar sample size yielded a significantly higher total at 80% (though the prevalence of HPV in invasive tumours was only 70%).[294] These data compare with those from earlier reports (1986-2000), which varied between 15 and 71%; the variation may be because of the sensitivity of detection methods, the influence of different cancer subtypes and geographical diversity.[295,296] The weighted average for HPV positivity from larger studies using a single detection method (polymerase chain

[289] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8.

[290] Gregoire L, Cubilla AL, Reuter VE et al. Preferential association of human papillomavirus with high-grade histologic variants of penile-invasive squamous cell carcinoma. *Journal of the National Cancer Institite.* 1995; 87(22): 1705-9. A 2001 result for warty carcinoma was somewhat lower, but still in excess of the HPV prevalence in squamous cell carcinoma. Bezerra AL, Lopes A, Landman G et al. Clinicopathologic features and human papillomavirus dna prevalence of warty and squamous cell carcinoma of the penis. *American Journal of Surgical Pathology.* 2001; 25(5): 673-8.

[291] Bunker CB. Topics in penile dermatology. *Clinical & Experimental Dermatology.* 2001; 26(6): 469-79.

[292] Across different studies, tthe variation in HPV prevalence for squamous cell carcinoma has been wide, from 5 to 48%. Melbye M, Frisch M. The role of human papillomaviruses in anogenital cancers. *Seminars in Cancer Biology.* 1998; 8(4): 307-13. A more recent result in a small sample was 67%. Humbey O, Cairey-Remonnay S, Guerrini JS et al. Detection of the human papillomavirus and analysis of the TP53 polymorphism of exon 4 at codon 72 in penile squamous cell carcinomas. *European Journal of Cancer.* 2003; 39(5): 684-90. In 2001, a study found HPV DNA in 30.5% of carcinomas. Bezerra AL, Lopes A, Santiago GH et al. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer.* 2001; 91(12): 2315-21.

[293] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8. This is quite close to the results reported from larger studies in a 1998 review. Melbye M, Frisch M. The role of human papillomaviruses in anogenital cancers. *Seminars in Cancer Biology.* 1998; 8(4): 307-13. The summary result of a 1995 review of over 20 studies was 48%. Cupp MR, Malek RS, Goellner JR et al. The detection of human papillomavirus deoxyribonucleic acid in intraepithelial, in situ, verrucous and invasive carcinoma of the penis. *Journal of Urology.* 1995; 154(3): 1024-9.

[294] Daling JR, Madeleine MM, Johnson LG et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *International Journal of Cancer.* 2005; 116(4): 606-16. A 2001 review suggested that 80% was the upper range for the prevalence of HPV in penile cancer. Bunker CB. Topics in penile dermatology. *Clinical & Experimental Dermatology.* 2001; 26(6): 469-79.

[295] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8.

[296] Cupp MR, Malek RS, Goellner JR et al. The detection of human papillomavirus deoxyribonucleic acid in intraepithelial, in situ, verrucous and invasive carcinoma of the penis. *Journal of Urology.* 1995; 154(3): 1024-9.

reaction, or PCR) was 52%.[297,298] The conclusion of a review of the literature from 1966 to 2000 was similar, namely, finding 40 to 50% HPV prevalence in penile cancer.[299]

As with other anogenital cancers, a variety of HPV types are detected.[300] However, HPV 16 dominates the story in both premalignant and malignant tumours, with HPV 18 being a distant second. The precise prevalence has varied across studies, as seen in the following table of larger studies.

Study	*Cancer Cases*	*HPV 16*	*HPV 18*	*HPV 16 and 18*	*Other types (including 6, 11, 31, 33, 35, 53)*
McCance et al. (1986)[301]	53			51%	
Iwasawa et al. (1993)[302]	123	57%	2%		
Cupp et al. (1995)[303]	42	40%	5%		12%
Levi et al. (1998)[304]	50	32%	6%		24%
Bezerra et al. (2001)[305]	82	16%	5%	1%	9%
Carter et al. (2001)[306]	33	70%	5%	Unclear	21%
Rubin et al. (2001)[307]	142	25%	1%		11%
Daling et al. (2005)[308]	94	69%		Unclear	8%

[297] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8.

[298] Daling JR, Madeleine MM, Johnson LG et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *International Journal of Cancer.* 2005; 116(4): 606-16. A smaller 2001 study (at 82%) matched this high rate. Carter JJ, Madeleine MM, Shera K et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. *Cancer Research.* 2001; 61(5): 1934-40.

[299] Dillner J, von Krogh G, Horenblas S et al. Etiology of squamous cell carcinoma of the penis. *Scandinavian Journal of Urology and Nephrology.* 2000; (205): 189-93.

[300] Meyer T, Arndt R, Christophers E et al. Association of rare human papillomavirus types with genital premalignant and malignant lesions. *Journal of Infectious Diseases.* 1998; 178(1): 252-5.

[301] McCance DJ, Kalache A, Ashdown K et al. Human papillomavirus types 16 and 18 in carcinomas of the penis from Brazil. *International Journal of Cancer.* 1986; 37(1): 55-9.

[302] Iwasawa A, Kumamoto Y, Fujinaga K. Detection of human papillomavirus deoxyribonucleic acid in penile carcinoma by polymerase chain reaction and in situ hybridization. *Journal of Urology.* 1993; 149(1): 59-63.

[303] Cupp MR, Malek RS, Goellner JR et al. The detection of human papillomavirus deoxyribonucleic acid in intraepithelial, in situ, verrucous and invasive carcinoma of the penis. *Journal of Urology.* 1995; 154(3): 1024-9.

[304] Levi JE, Rahal P, Sarkis AS et al. Human papillomavirus DNA and p53 status in penile carcinomas. *International Journal of Cancer.* 1998; 76(6): 779-83.

[305] Bezerra AL, Lopes A, Santiago GH et al. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer.* 2001; 91(12): 2315-21.

[306] Carter JJ, Madeleine MM, Shera K et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. *Cancer Research.* 2001; 61(5): 1934-40.

[307] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8.

The preceding percentages use the total the number of cancer cases as the denominator. If restricted to HPV positive cases, the percentage of type 16 varies from 52% to almost 90%.

A complex "cocktail" of HPV types can be detected in tumours; in the study by Rubin and others, only 30% of the cases presented with a single HPV type—almost always one of the "high-risk" varieties.[309] Surprisingly, the mixed situations sometimes involve types 6 and 11, considered to be low-risk and usually associated with noncarcinogenic warts (see below).[310] Finally, some specific associations are emerging in the literature; for example, HPV 8 has been strongly linked to erythroplasia of Queyrat.[311]

Summing up the evidence, a conservative "rule of thumb" for penile cancer would be that HPV infection is involved with half the cases, with 50 to 60% of those reflecting the presence of HPV 16 specifically.

Cancer of the Anus

Description

The anal canal extends from the true skin of the anal margin or verge to the rectum (approximately the last 4-5 cm. of the digestive tract). The region of the anal canal where squamous mucosal cells transition into the rectal mucosa, sometimes called the dentate line, is a zone at high risk for cancer.[312] Neoplasia can also occur in other locations, including the skin surrounding the anus.

The most common type of anal cancer is squamous cell carcinoma (about 75 to 80% of cases). Adenocarcinomas account for up to 19% of cases, while the basaloid variant of squamous cell carcinoma and melanomas occur more rarely.[313,314] Since they have a different prognosis and management strategy, cancers involving the skin cells at the most distal end of the canal are sometimes distinguished as anal margin carcinoma.[315,316] The remaining, more distal anal canal malignancies are sometimes

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[308] Daling JR, Madeleine MM, Johnson LG et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *International Journal of Cancer.* 2005; 116(4): 606-16.

[309] Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *American Journal of Pathology.* 2001; 159(4): 1211-8.

[310] Turazza E, Lapena A, Sprovieri O et al. Low-risk human papillomavirus types 6 and 11 associated with carcinomas of the genital and upper aero-digestive tract.*Acta Obstetricia et Gynecologica Scandinavica.* 1997; 76(3): 271-6.

[311] Wieland U, Jurk S, Weissenborn S et al. Erythroplasia of queyrat: coinfection with cutaneous carcinogenic human papillomavirus type 8 and genital papillomaviruses in a carcinoma in situ. *Journal of Investigative Dermatology.* 2000; 115(3): 396-401.

[312] Ryan DP, Mayer RJ. Anal carcinoma: histology, staging, epidemiology, treatment. *Current Opinion in Oncology.* 2000; 12(4): 345-52.

[313] Moore HG, Guillem JG. Anal neoplasms. *Surgical Clinics of North America.* 2002; 82(6): 1233-51.

[314] Esiashvili N, Landry J, Matthews RH. Carcinoma of the anus: strategies in management. *The Oncologist.* 2002; 7(3): 188-99.

[315] Ryan DP, Mayer RJ. Anal carcinoma: histology, staging, epidemiology, treatment. *Current Opinion in Oncology.* 2000; 12(4): 345-52.

[316] Gervasoni JE, Jr., Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Investigation.* 2003; 21(3): 452-64.

aggregated with colorectal or anorectal cancers, of which they comprise a small proportion (variously reported as 1 to 10%).[317,318,319,320]

Anal intraepithelial neoplasia (AIN) is the beginning of a progressive cellular change leading to squamous cell carcinoma. AIN is graded similarly to other genital cancers, from a subclinical infection with high-risk HPV types through low-grade squamous intraepithelial lesions to high-grade lesions and finally invasive anal cancer.[321]

While topical treatments are being tried for AIN, anal canal cancers are usually managed with radiation or chemotherapy or both, or any of these in combination with radical surgery. While resection used to be standard, the current preference is to start with conservative approaches, restricting surgery to a salvage procedure in order to forestall serious consequences such as a permanent colostomy.[322,323,324] This strategy is effective even in advanced disease.[325] The 5 year survival rate for traditional surgery (40 to70%)[326] is being matched by the newer combination therapies involving chemoradiation; for example, Cummings et al. demonstrated a 65% survival over a 69 patient series,[327] while more recent studies have posted even better results.[328,329]

Tumor size and the degree of nodal involvement influence prognosis. Lesions less than 2 cm. can be cured 80% of the time; if the lesion is 5 cm. or more, the rate drops below 50%.[330] The type of cancer is also important; anal melanomas, though rare, are particularly lethal.[331,332]

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[317] Moore HG, Guillem JG. Anal neoplasms. *Surgical Clinics of North America.* 2002; 82(6): 1233-51.
[318] Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *The Lancet.* 2004; 5(3): 149-57.
[319] Esiashvili N, Landry J, Matthews RH. Carcinoma of the anus: strategies in management. *The Oncologist.* 2002; 7(3): 188-99.
[320] Gervasoni JE, Jr., Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Investigation.* 2003; 21(3): 452-64.
[321] Martin F, Bower M. Anal intraepithelial neoplasia in HIV positive people. *Sexually Transmitted Infections.* 2001; 77(5): 327-31.
[322] Esiashvili N, Landry J, Matthews RH. Carcinoma of the anus: strategies in management. *The Oncologist.* 2002; 7(3): 188-99.
[323] Eng C, Abbruzzese J, Minsky BD. Chemotherapy and radiation of anal canal cancer: the first approach. *Surgical oncology clinics of North America.* 2004; 13(2): 309-20, viii.
[324] Gervaz P, Allal AS, Roth A et al. Chemotherapeutic options in the management of anal cancer. *Expert Opinion in Pharmacotherapy.* 2004; 5(12): 2479-84.
[325] Mitchell SE, Mendenhall WM, Zlotecki RA et al. Squamous cell carcinoma of the anal canal. *International Journal of Radiation Oncology, Biology, Physics.* 2001; 49(4): 1007-13.
[326] Ryan DP, Mayer RJ. Anal carcinoma: histology, staging, epidemiology, treatment. *Current Opinion in Oncology.* 2000; 12(4): 345-52.
[327] Cummings BJ, Keane TJ, O'Sullivan B et al. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. *International Journal of Radiation Oncology, Biology, Physics.* 1991; 21(5): 1115-25.
[328] Faynsod M, Vargas HI, Tolmos J et al. Patterns of recurrence in anal canal carcinoma. *Archives of Surgery.* 2000; 135(9): 1090-3; discussion 4-5.
[329] Kapp KS, Geyer E, Gebhart FH et al. Experience with split-course external beam irradiation +/- chemotherapy and integrated Ir-192 high-dose-rate brachytherapy in the treatment of primary carcinomas of the anal canal. *International Journal of Radiation Oncology, Biology, Physics.* 2001; 49(4): 997-1005.
[330] Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *New England Journal of Medicine.* 2000; 342(11): 792-800.
[331] Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *The Lancet.* 2004; 5(3): 149-57.

Research on anal cancer has been intensifying as the similarity and connection with cervical cancer becomes more evident.[333,334] An example of the latter is the fact that women with a diagnosis of anal cancer are more likely to have had cervical, vulvar, or vaginal cancer.[335] One important issue related to anal cancer is the "delay in diagnosis due to confusion with more common, benign conditions."[336] In this connection, preventive screening measures equivalent to the Pap smear are being pursued to diminish the number of anal cancer cases.[337] Despite this focus, there is evidence that anal cancer rates are increasing in some countries, especially among younger men.[338,339,340] Some of this increase is attributable to the rising incidence of anal neoplasia seen among men having sex with men and among all people with HIV infection (see below).[341,342,343]

Epidemiology

The annual incidence of anal cancer is about 1 per 100,000 in the heterosexual population, resulting in approximately 3,500 to 4,000 new cases each year in the US.[344,345] Historically, there has been a female predominance in anal cancer, though the scales seem to be tipping towards men. Males already have the highest incidence in the younger age group.[346]

The most important risk factors are directly related to sexual practices and not necessarily sexual preference or gender per se.[347] Heterosexual men are more at risk when 10 or more sexual partners have been reported and there is a history of genital

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[332] Gervasoni JE, Jr., Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Investigation.* 2003; 21(3): 452-64.

[333] Zbar AP, Fenger C, Efron J et al. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. *International Journal of Colorectal Disease.* 2002; 17(4): 203-15.

[334] Gervaz P, Allal AS, Villiger P et al. Squamous cell carcinoma of the anus: another sexually transmitted disease. *Swiss Medical Weekly.* 2003; 133(25-26): 353-9.

[335] Holly EA, Ralston ML, Darragh TM et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *Journal of the National Cancer Institute.* 2001; 93(11): 843-9.

[336] Moore HG, Guillem JG. Anal neoplasms. *Surgical Clinics of North America.* 2002; 82(6): 1233-51.

[337] Mathews WC. Screening for anal dysplasia associated with human papillomavirus. *Topics in HIV Medicine.* 2003; 11(2): 45-9.

[338] Gervasoni JE, Jr., Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Investigation.* 2003; 21(3): 452-64.

[339] Frisch M. On the etiology of anal squamous carcinoma. *Danish Medical Bulletin.* 2002; 49(3): 194-209.

[340] Johnson LG, Madeleine MM, Newcomer LM et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer.* 2004; 101(2): 281-8.

[341] Chin-Hong PV, Vittinghoff E, Cranston RD et al. Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. *Journal of the National Cancer Institute.* 2005; 97(12): 896-905.

[342] Holly EA, Ralston ML, Darragh TM et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *Journal of the National Cancer Institute.* 2001; 93(11): 843-9.

[343] Sobhani I, Walker F, Aparicio T et al. Effect of anal epidermoid cancer-related viruses on the dendritic (Langerhans') cells of the human anal mucosa. *Clinical Cancer Research.* 2002; 8(9): 2862-9.

[344] Gervasoni JE, Jr., Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Investigation.* 2003; 21(3): 452-64.

[345] Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *The Lancet.* 2004; 5(3): 149-57.

[346] Johnson LG, Madeleine MM, Newcomer LM et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer.* 2004; 101(2): 281-8.

[347] Frisch M. On the etiology of anal squamous carcinoma. *Danish Medical Bulletin.* 2002; 49(3): 194-209.

warts, syphilis, or hepatitis; overall, though, men with anal cancer are more likely to have engaged in sex with other men, to have practiced anal intercourse, and to have a history of genital warts. The incidence of anal cancer among men practicing anal-receptive sexual intercourse is as much as 35 per 100,000.[348]

The presence of HIV infection increases the risk of developing anal cancer for at least two reasons: as a correlative factor related to the transmission of HPV through risky sexual activity and as an etiologic factor related to immunosuppression.[349] A possible direct HIV-HPV interaction has also been postulated.[350,351] There may be another unexpected force at work in rising incidence rates, one which has resulted from effective HIV / AIDS therapies, namely, the fact that increased longevity has expanded the opportunity for malignancies to develop.[352] Greater use of cytological screening may also be playing a role in detecting more anal cancers.[353,354]

The only consistently observed non-sexual risk factor for anal cancer is smoking.[355,356]

Relationship to HPV

Anal cancer is etiologically more closely related to cancers of the genital region than to those of the digestive tract.[357] Opinions concerning the cause of anal cancer, once focused on chronic irritation from sources such as hemorrhoids, fissures, and inflammatory bowel disease, have shifted as the evidence of a sexually transmitted agent, namely HPV, has accumulated.[358] The rate of detection of the virus has varied widely in older studies (0 to 85%).[359] The following table compares recent results from three larger studies which examined the prevalence of HPV in anal tumors.

[348] Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *The Lancet.* 2004; 5(3): 149-57.
[349] Gervaz P, Allal AS, Villiger P et al. Squamous cell carcinoma of the anus: another sexually transmitted disease. *Swiss Medical Weekly.* 2003; 133(25-26): 353-9.
[350] Panther LA, Schlecht HP, Dezube BJ. Spectrum of human papillomavirus-related dysplasia and carcinoma of the anus in HIV-infected patients. *AIDS Reader.* 2005; 15(2): 79-82, 5-6, 8, 91.
[351] Sobhani I, Walker F, Aparicio T et al. Effect of anal epidermoid cancer-related viruses on the dendritic (Langerhans') cells of the human anal mucosa. *Clinical Cancer Research.* 2002; 8(9): 2862-9.
[352] Martin F, Bower M. Anal intraepithelial neoplasia in HIV positive people. *Sexually Transmitted Infections.* 2001; 77(5): 327-31.
[353] Diamond C, Taylor TH, Aboumrad T et al. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sexually Transmitted Diseases.* 2005; 32(5): 314-20.
[354] Johnson LG, Madeleine MM, Newcomer LM et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer.* 2004; 101(2): 281-8.
[355] Frisch M. On the etiology of anal squamous carcinoma. *Danish Medical Bulletin.* 2002; 49(3): 194-209.
[356] Daling JR, Madeleine MM, Johnson LG et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer.* 2004; 101(2): 270-80.
[357] Johnson LG, Madeleine MM, Newcomer LM et al. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer.* 2004; 101(2): 281-8.
[358] Daling JR, Weiss NS, Hislop TG et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *New England Journal of Medicine.* 1987; 317(16): 973-7.
[359] Holm R, Tanum G, Karlsen F et al. Prevalence and physical state of human papillomavirus DNA in anal carcinomas. *Modern Pathology.* 1994; 7(4): 449-53.

Lead author	*Sample Size*	*HPV positive*	*HPV 16 (% of positive cases)*	*HPV 18*	*Other types*
Holm (1994)[360]	99	81%	93%		
Frisch (1997)[361]	388	88%	82%	6%	12%
Daling (2004)[362]	306	88%	73%	7%	

In sum, the very high proportion of neoplasia with detectable HPV (especially type 16) suggests that the virus is a necessary cause of anal cancer, similar to the situation with cervical cancer.[363]

[360] Holm R, Tanum G, Karlsen F et al. Prevalence and physical state of human papillomavirus DNA in anal carcinomas. *Modern Pathology.* 1994; 7(4): 449-53.
[361] Frisch M, Glimelius B, van den Brule AJ et al. Sexually transmitted infection as a cause of anal cancer. *New England Journal of Medicine.* 1997; 337(19): 1350-8.
[362] Daling JR, Madeleine MM, Johnson LG et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer.* 2004; 101(2): 270-80.
[363] Daling JR, Madeleine MM, Johnson LG et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer.* 2004; 101(2): 270-80.

Cancers of the Head and Neck

HPV DNA has been detected in a wide variety of nongenital human cancers, notably among tissues of the head and neck.[364] Data supporting a link between HPV and oropharangeal cancers are the most compelling.[365] Specific head and neck sites of interest include the larynx, the tonsils and the oral cavity itself.[366] We will include ocular cancers under this category, though they are normally considered separately. Among the major cancers, the survival rate for head and neck cancers is one of the poorest. This is because the early signs are frequently missed or ignored, so that a case of head and neck cancer often presents in an advanced stage that is not very amenable to treatment. This clinical reality suggests that preventive measures would be very welcome. As investigation of the causation of such cancers continues, researchers are keen to ensure that proposed viral associations "fit coherently within our current framework of knowledge of the epidemiology and biology of HPV infection."[367]

Cancer of the Larynx

Description

The larynx is a complex part of the respiratory tract between the oropharynx (the throat, or the back of the mouth and nose, where food and air cross) and the trachea (the windpipe leading to the lungs); the larynx, recognized externally as the so-called Adam's apple, is the main organ of voice production.

Cancer of the larynx is the most common head and neck malignancy apart from skin cancer; the larynx is the site of 20% of head and neck cancers in the US (excluding the skin).[368] Although physicians knew about laryngeal tumours even in ancient times, it was not until the mid 19th century that examination of this part of the body was made possible through the development of a prototype of the laryngoscope.[369]

The most common benign laryngeal neoplasm is papilloma,[370] accounting for 84% of such tumours.[371] Overall, laryngeal papillomatosis (also known as respiratory papillomatosis; see below) is rare; one Danish study reported an annual incidence of

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[364] Venuti A, Manni V, Morello R et al. Physical state and expression of human papillomavirus in laryngeal carcinoma and surrounding normal mucosa. *Journal of Medical Virology.* 2000; 60(4): 396-402.

[365] Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. *Journal of the National Cancer Institute Monographs.* 2003; (31): 57-65.

[366] Major T, Szarka K, Sziklai I et al. The characteristics of human papillomavirus DNA in head and neck cancers and papillomas. *Journal of Clinical Pathology.* 2005; 58(1): 51-5.

[367] Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. *Journal of the National Cancer Institute Monographs.* 2003; (31): 57-65.

[368] Hoffman HT, Karnell LH, Funk GF et al. The National Cancer Data Base report on cancer of the head and neck. *Archives of Otolaryngology - Head & Neck Surgery.* 1998; 124(9): 951-62.

[369] Rafferty MA, Fenton JE, Jones AS. The history, aetiology and epidemiology of laryngeal carcinoma. *Clinical Otolaryngology & Allied Sciences.* 2001; 26(6): 442-6.

[370] A tumour resulting from an overgrowth of epithelial tissue on papillae of vascularized connective tissue. The general term given to tumours of the skin or mucosa, including the well-known wart or condyloma. Can be used to specifically refer to the disease known as papillomatosis, characterized by multiple, small tumours.

[371] Jones SR, Myers EN, Barnes L. Benign neoplasms of the larynx. *Otolaryngologic Clinics of North America.* 1984; 17(1): 151-78.

3.8 per million people.[372] Malignant transformation of papillomas is also infrequent, occurring in only 3 to 7% of cases.[373]

As with many HPV-related cancers, squamous cell carcinoma is the most common type of laryngeal malignancy; other known forms include sarcomas and lymphomas, but these are extremely rare.[374,375,376] Sometimes it is important to distinguish variants of squamous cell carcinoma; for example, basaloid squamous cell carcinoma can be a highly aggressive tumour requiring serious intervention when detected in the larynx or in other sites.[377] Verrucous carcinoma, in contrast, is a well-differentiated variant with low malignant potential.[378]

Another important differentiation with regard to laryngeal cancer is anatomical: where precisely does the cancer appear in the three regions of the larynx (usually denoted as the glottis,[379] supraglottis and subglottis)? Unfortunately, the borders of these regions as observed through imaging remain controversial, complicating the identification and staging of tumours.[380,381] The distinctions become important in research, treatment and prognosis.[382,383] For example, primary subglottic cancer is often highly malignant, with a poor prognosis that is sometimes exacerbated by delayed detection; fortunately, primary cancer at this site only accounts for 1 to 8% of laryngeal cancers.[384] Sometimes cancer crosses boundaries and affects more than one area of the larynx (so-called transglottic cancer); the prognosis in such cases is usually poorer than with disease localized in the vocal cords.[385]

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[372] Aaltonen LM, Rihkanen H, Vaheri A. Human papillomavirus in larynx. *Laryngoscope.* 2002; 112(4): 700-7.

[373] Lie ES, Engh V, Boysen M et al. Squamous cell carcinoma of the respiratory tract following laryngeal papillomatosis. *Acta Otolaryngologica.* 1994; 114(2): 209-12.

[374] Miura K, Kum Y, Han G et al. Radiation-induced laryngeal angiosarcoma after cervical tuberculosis and squamous cell carcinoma: case report and review of the literature. *Pathology International.* 2003; 53(10): 710-5.

[375] Palenzuela G, Bernard F, Gardiner Q et al. Malignant B cell non-Hodgkin's lymphoma of the larynx in children with Wiskott Aldrich syndrome. *International Journal of Pediatric Otorhinolaryngology.* 2003; 67(9): 989-93.

[376] King AD, Yuen EH, Lei KI et al. Non-Hodgkin lymphoma of the larynx: CT and MR imaging findings. *AJNR American Journal of Neuroradiology.* 2004; 25(1): 12-5.

[377] Bahar G, Feinmesser R, Popovtzer A et al. Basaloid squamous carcinoma of the larynx. *American Journal of Otolaryngology.* 2003; 24(3): 204-8. But see the contrary assessment in Erisen LM, Coskun H, Ozuysal S et al. Basaloid squamous cell carcinoma of the larynx: a report of four new cases. *Laryngoscope.* 2004; 114(7): 1179-83.

[378] Aaltonen LM, Rihkanen H, Vaheri A. Human papillomavirus in larynx. *Laryngoscope.* 2002; 112(4): 700-7.

[379] The middle region of the larynx, consisting of the vocal cords and the opening between them.

[380] Ferlito A, Rinaldo A. The pathology and management of subglottic cancer. *European Archives of Otorhinolaryngology.* 2000; 257(3): 168-73.

[381] Strome SE, Robey TC, Devaney KO et al. Subglottic carcinoma: review of a series and characterization of its patterns of spread. *Ear, Nose, & Throat Journal.* 1999; 78(8): 622-4, 6, 8, passim.

[382] De Stefani E, Boffetta P, Deneo-Pellegrini H et al. Supraglottic and glottic carcinomas: epidemiologically distinct entities? *International Journal of Cancer.* 2004; 112(6): 1065-71.

[383] Filho VW. The epidemiology of laryngeal cancer in Brazil. *Sao Paulo Medical Journal.* 2004; 122(5): 188-94.

[384] Su WF, Jen YM, Nieh S. Multifocal carcinoma of the larynx presenting as subglottic carcinoma. *European Archives of Otorhinolaryngology.* 2003; 260(4): 211-5.

[385] Leon X, Quer M, de Juan M et al. [Differential features of transglottic carcinoma]. *Acta Otorrinolaringologica Espanola.* 1998; 49(7): 569-75.

Following the usual pattern for cancer, treatment of laryngeal cancer depends especially on staging. In early stages, where glottic cancers especially are highly curable, conservative approaches such as radiotherapy are employed; small tumours that do not impair vocal cord mobility can be treated by laser excision. In later stages, salvage surgery or partial laryngectomy may still allow voice preservation. Total laryngectomy is usually reserved for persistent or recurrent disease;[386] the recurrence rate following radiotherapy can in fact be as high as 50%.[387] Routine removal of neck lymph nodes in advanced cancer or more aggressive forms such as supraglottic carcinoma is recommended by some specialists, but this remains controversial.[388,389] Other clinicians are exploring the optimization of conservative strategies, including chemotherapy, in these types of cancer.[390,391]

Again, as with other cancers, survival rates in laryngeal cancer relate to staging. As one editorial noted, "early detection appears to be the best and only chance to improve the therapeutic results."[392] One 2004 study of over 1,100 Chinese patients revealed the following data:[393]

Stage	*Five year survival rate*
I	94%
II	89
III	82
IV	66

Overall 5-year survival was 77%. This result was somewhat lower than other published data, e.g., 88% in an Israeli series,[394] 90% for glottic cancer in a Spanish study,[395] and 87 to 89% in two limited female series, though higher than pan-European figures for 1989 (63%). The 5-year survival rate seen across the whole

[386] Sasaki CT, Jassin B. Cancer of the pharynx and larynx. *American Journal of Medicine.* 2001; 111 Suppl 8A: 118S-23S.
[387] Guo ZM, Zeng ZY, Chen FJ et al. [Factoral analysis related to primary recurrence of laryngeal squamous cell carcinomas after treatment]. *Ai Zheng.* 2002; 21(10): 1081-4.
[388] Pinilla M, Gonzalez FM, Lopez-Cortijo C et al. Management of N0 neck in laryngeal carcinoma. Impact on patient's survival. *Journal of Laryngology & Otology.* 2003; 117(1): 63-6.
[389] Ferlito A, Silver CE, Rinaldo A et al. Surgical treatment of the neck in cancer of the larynx. *ORL Journal of Oto-Rhino-Laryngology & its Related Specialties.* 2000; 62(4): 217-25.
[390] Jorgensen K, Godballe C, Hansen O et al. Cancer of the larynx--treatment results after primary radiotherapy with salvage surgery in a series of 1005 patients. *Acta Oncologica.* 2002; 41(1): 69-76.
[391] Ljumanovic R, Langendijk JA, Schenk B et al. Supraglottic carcinoma treated with curative radiation therapy: identification of prognostic groups with MR imaging. *Radiology.* 2004; 232(2): 440-8.
[392] Ferlito A, Doglioni C, Rinaldo A et al. What is the earliest non-invasive malignant lesion of the larynx? *ORL Journal of Oto-Rhino-Laryngology & its Related Specialties.* 2000; 62(2): 57-9.
[393] Ji WY, Du Q, Guan C et al. [Survival analysis of 1115 patients with laryngeal carcinoma]. *Chinese Journal of Otorhinolaryngology.* 2004; 39(1): 17-9.
[394] Brenner B, Marshak G, Rakowsky E et al. Laryngeal carcinoma--epidemiological and clinical features: experience of the Rabin Medical Center in Israel. *Oncology Reports.* 2001; 8(1): 141-4.
[395] Leon X, Quer M, de Juan M et al. [Differential features of transglottic carcinoma]. *Acta Otorrinolaringologica Espanola.* 1998; 49(7): 569-75.

world is commonly quoted as 60 to 65%, for all types and treatments.[396] This is consistent with the rate reported in B.C. in 1996, namely, 64%.[397]

Epidemiology
The incidence of laryngeal cancer is relatively low, though there are some notable exceptions, e.g., Brazil, Poland and Spain. The annual age-adjusted incidence rate is less than 5 per 100,000 in Sweden, for instance, but over double that figure in Sao Paulo and Warsaw.[398] Cancer of the larynx accounts for 1 to 2% of all new cancer cases in the world each year.

Laryngeal cancer afflicts more men than women; indeed, it is the eleventh commonest male cancer worldwide.[399] The incidence rate for men in southern Europe is as high as 18 per 100,000.[400] The 2005 global estimates for new cases are 160,000 for men and 22,000 for women, representing one of the highest gender differentials for any cancer site. Around 89,000 men will die of the disease in 2005.[401]

Laryngeal cancer is commonest in the 50 to 70 age range; for example, a review in Brazil showed that 63% of the cases occurred among this cohort.[402]

Cancer of the larynx has consistently been strongly associated with tobacco smoking and alcohol consumption, with smoking as the dominant behavioral risk factor. Some studies suggest a synergistic effect on cancer development when both behaviours are present.[403] An estimated 90 to 95% of laryngeal cancers could be prevented if tobacco and alcohol were avoided.[404] Certain nutrients found in fruit and vegetables may be protective,[405] while asbestos and other occupational exposures may promote cancer of the larynx (though this remains controversial).[406] Gastroesophageal reflux also appears to be a carcinogenic co-factor. Finally, certain genetic susceptibilities for cancer of the larynx are being investigated.

Incidence trends mainly follow the changing pattern of tobacco and alcohol use.[407] Thus the occurrence of laryngeal cancer is generally declining in Finland, which has

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[396] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[397] Data available at www.bccancer.bc.ca. Accessed August 2005.
[398] Filho VW. The epidemiology of laryngeal cancer in Brazil. *Sao Paulo Medical Journal.* 2004; 122(5): 188-94.
[399] Rafferty MA, Fenton JE, Jones AS. The history, aetiology and epidemiology of laryngeal carcinoma. *Clinical Otolaryngology & Allied Sciences.* 2001; 26(6): 442-6.
[400] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[401] Filho VW. The epidemiology of laryngeal cancer in Brazil. *Sao Paulo Medical Journal.* 2004; 122(5): 188-94.
[402] Filho VW. The epidemiology of laryngeal cancer in Brazil. *Sao Paulo Medical Journal.* 2004; 122(5): 188-94.
[403] Flanders WD, Rothman KJ. Interaction of alcohol and tobacco in laryngeal cancer. *American Journal of Epidemiology.* 1982; 115(3): 371-9.
[404] Rafferty MA, Fenton JE, Jones AS. The history, aetiology and epidemiology of laryngeal carcinoma. *Clinical Otolaryngology & Allied Sciences.* 2001; 26(6): 442-6.
[405] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[406] Rafferty MA, Fenton JE, Jones AS. The history, aetiology and epidemiology of laryngeal carcinoma. *Clinical Otolaryngology & Allied Sciences.* 2001; 26(6): 442-6.
[407] Tuyns AJ. Laryngeal cancer. *Cancer Surveys.* 1994; 19-20: 159-73.

experienced a significant decrease in smoking prevalence in recent decades.[408] In contrast, there is a suggestion that overall laryngeal cancer rates may be increasing worldwide, notably in central and eastern Europe and among women in North America.[409]

A Canadian experience is provided by the University of Alberta, which reviewed 379 cases over 15 years. Males comprised 88% and females 12% of the cases, with average age being 59 years.[410]

A total of 93 new cases of laryngeal cancer were reported in B.C. in 2003.

Relationship to HPV
A 2002 review summed up the current state of affairs, namely, that the "role of HPV in laryngeal carcinogenesis remains unclear."[411] While virtually all benign laryngeal papillomas (see below under recurrent respiratory papillomatosis) contain HPV 6 and 11,[412,413] malignant transformation of these lesions is an uncommon event, occurring in only 3 to 7% of patients.[414]

Up to 15% of laryngeal carcinomas contain HPV; one small study demonstrated HPV positivity of just over 50%.

The carcinomas from papilloma patients generally harbour the same type of HPV DNA seen in benign tumours, namely, type 6 and 11.[415] Different studies have detected other HPV variants, including types 16[416] and 18.[417]

The present research suggests that HPV may be involved with some cases of laryngeal carcinoma, but with transformation mechanisms possibly different than in anogenital cancer.[418]

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[408] Teppo H, Koivunen P, Sipila S et al. Decreasing incidence and improved survival of laryngeal cancer in Finland. *Acta Oncologica.* 2001; 40(7): 791-5.
[409] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[410] Marck PA, Lupin AJ. Cancer of the larynx: the northern Alberta experience. *Journal of Otolaryngology.* 1989; 18(7): 344-9.
[411] Aaltonen LM, Rihkanen H, Vaheri A. Human papillomavirus in larynx. *Laryngoscope.* 2002; 112(4): 700-7.
[412] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[413] Balukova OV, Shcherbak LN, Savelov NA et al. [Papilloma virus infection in pretumor and tumor masses of the larynx]. *Vestnik Rossiiskoi Akademii Meditsinskikh.* 2004; (12): 36-9.
[414] Aaltonen LM, Rihkanen H, Vaheri A. Human papillomavirus in larynx. *Laryngoscope.* 2002; 112(4): 700-7.
[415] Licitra L, Bernier J, Grandi C et al. Cancer of the larynx. *Critical Reviews in Oncology / Hematology.* 2003; 47(1): 65-80.
[416] Venuti A, Manni V, Morello R et al. Physical state and expression of human papillomavirus in laryngeal carcinoma and surrounding normal mucosa. *Journal of Medical Virology.* 2000; 60(4): 396-402.
[417] Balukova OV, Shcherbak LN, Savelov NA et al. [Papilloma virus infection in pretumor and tumor masses of the larynx]. *Vestnik Rossiiskoi Akademii Meditsinskikh.* 2004; (12): 36-9.
[418] Venuti A, Manni V, Morello R et al. Physical state and expression of human papillomavirus in laryngeal carcinoma and surrounding normal mucosa. *Journal of Medical Virology.* 2000; 60(4): 396-402.

Oral Cancers

Description

Any discussion of oral cancers must begin with clear definitions because of the complexity and proximity of the multiple passages in what is sometimes known as the upper aerodigestive tract. For instance, where exactly does the mouth end and the throat begin? Researchers use different schemes to aggregate the anatomical areas and related cancers in this part of the head and neck. For example, it is common to speak of oropharyngeal cancers. For our purposes, we will consider oral cancer to include malignancies in the oral cavity, the palatine tonsils (covered below), and the rest of the oropharynx.

Each of these areas has its own subdivisions. The oral cavity proper (commonly called the mouth) comprises the lips, lining of the cheeks (or buccal mucosa), hard palate, and floor of the mouth. Sometimes the anterior tongue, gums and salivary glands are included. The oropharynx is the middle part of the pharynx or, as the "oro-" in its name suggests, that part which is visible upon normal inspection of the "back of the mouth." It is traditionally considered to include the soft palate, the base of the tongue (with the lingual tonsils), and sometimes the palatine tonsils, commonly known as simply the tonsils. Most of the following information will focus on the oral cavity, as most of the research in the oropharyngeal area is subsumed under the topic of the tonsils (see below). In the interest of moderating the length of this report, the tongue will not be specifically assessed.

Squamous cell carcinoma accounts for 95% of the malignancies in the oral cavity.[419] It represents a significant problem because of its relatively high incidence (see below) and unsatisfactory treatment outcomes, including severe functional and cosmetic defects. In one study of almost 400 patients, the 5 year survival rate for stage III and IV carcinomas was less than 50%.[420]

Epidemiology

The anatomical discussion above points out the complexity of assembling and comparing epidemiological and etiological data. Sometimes, contrary to the usage we just described, "oral" and "oropharyngeal" are distinguished by researchers.[421]

An analysis by Franceschi et al. revealed that oral cavity cancer incidence in Canada (1988-92) was 4.9 per 100,000 males and 1.9 per 100,000 females.[422] Another study, which combined oral cavity and pharyneal cancers, reported a global rate of 8.3 per 100,000 in 1994-98.[423] In 2001, this was reflected in over 30,000 new cases in the US.

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[419] Lo WL, Kao SY, Chi LY et al. Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. *Journal of Oral & Maxillofacial Surgery.* 2003; 61(7): 751-8.
[420] Lo WL, Kao SY, Chi LY et al. Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. *Journal of Oral & Maxillofacial Surgery.* 2003; 61(7): 751-8.
[421] Kreimer AR, Clifford GM, Snijders PJ et al. HPV16 semiquantitative viral load and serologic biomarkers in oral and oropharyngeal squamous cell carcinomas. *International Journal of Cancer.* 2005; 115(2): 329-32.
[422] Franceschi S, Bidoli E, Herrero R et al. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral Oncology.* 2000; 36(1): 106-15.
[423] Canto MT, Devesa SS. Oral cavity and pharynx cancer incidence rates in the United States, 1975-1998. *Oral Oncology.* 2002; 38(6): 610-7.

The major risk factors for oral cancers are the use of tobacco products and excessive alcohol consumption, estimated to account for 75% of all oral and pharyngeal cancers.[424] One study concluded that "simultaneous exposure to tobacco and alcohol consumption increases oral cancer risk in a synergistic fashion, even when consumption levels are moderate."[425] However, there are individuals who develop oral cancer in the absence of these behavioural factors; evidence has been accumulating that a sexually transmitted agent, specifically HPV, is also involved in at least a subset of oral tumours.[426]

Relationship to HPV

There appears to be a stronger link between HPV and oropharyngeal cancers compared to oral cavity cancers. A major study found HPV DNA in 3.9% of 766 oral cavity cancers, while the virus was detected in 18.3% of 142 cases of cancer in the oropharynx (including the tonsils).[427] A review in 2005 indicated that 22% of oral cancers that had been analysed for HPV were found to be positive.[428] As we will see in the discussion of tonsillar cancer, HPV 16 dominates in the etiology of oropharangeal cancers, while this viral type is seldom found in the case of oral cavity malignancies.[429]

Cancer of the Tonsils

Description

The tonsils, more properly the palatine tonsils, are two small lumps of lymphatic tissue located in the throat at the back of the mouth (i.e., in the so-called oropharynx—see above). The term "tonsil" is sometimes applied to other lymphatic tissue in the pharynx, including the adenoids, otherwise termed the nasopharyngeal, or simply the pharyngeal, tonsils. Taken together, the circle of tonsillar lymphatic tissue, protecting against pathogens at this "crossroads" region where air and food pass into the body, is known as Waldeyer's ring.

Tonsillar cancer traditionally has been reported as the most common of the oropharyngeal malignancies, representing 15 to 20% of all such cancers in the US.[430] However, this conclusion is complicated by varying classification systems (which

[424] Blot WJ, McLaughlin JK, Winn DM et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research.* 1988; 48(11): 3282-7.
[425] Castellsague X, Quintana MJ, Martinez MC et al. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. *International Journal of Cancer*. 2004; 108(5): 741-9.
[426] Smith EM, Ritchie JM, Summersgill KF et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. *International Journal of Cancer*. 2004; 108(5): 766-72.
[427] Herrero R, Castellsague X, Pawlita M et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *Journal of the National Cancer Institute.* 2003; 95(23): 1772-83.
[428] Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *Journal of Clinical Virology.* 2005; 32 Suppl 1: S59-66.
[429] Ha PK, Pai SI, Westra WH et al. Real-time quantitative PCR demonstrates low prevalence of human papillomavirus type 16 in premalignant and malignant lesions of the oral cavity. *Clinical Cancer Research.* 2002; 8(5): 1203-9.
[430] Frisch M, Hjalgrim H, Jaeger AB et al. Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control.* 2000; 11(6): 489-95.

include more or fewer of the tonsillar and related sites and of the different types of cancer).

There is evidence that the occurrence of tonsillar cancer is on the rise in some locations (see below).

The most common tumour of the palatine tonsils is squamous cell carcinoma (over 80% of cases), followed by lymphoma (up to 16%).[431] Cases of tonsillar squamous cell carcinoma accounts for 15 to 23% of all oropharyngeal squamous cell carcinomas.[432] Outside of the lymph nodes, Waldeyer's ring is the most common site for non-Hodgkin's lymphoma in the head and neck; more specifically, up to 80% of such cases are localized in the tonsils.[433] Other rarer forms of tonsillar cancer exist, including melanoma,[434] sarcoma, and salivary gland malignancies.

One review noted that "the management of tonsillar cancer remains challenging and without a uniform consensus."[435] As with most cancers, the most often recommended therapy varies with staging. Early-stage squamous cell carcinoma is responsive to radiation therapy alone, whereas the classic treatment for patients with advanced tonsillar cancer involves surgery followed by radiation therapy and/or chemotherapy. Recently, irradiation followed by salvage therapy has been promoted as an alternate approach[436] One study of 84 surgeries demonstrated survival rates of 89% for stage I, 91% for stage II, 79% for stage III, and 52% for stage IV cancer.[437] Many have reported the fact that the prognosis for tonsillar cancer tends to be better when HPV is detected, possibly indicating the role of an active antiviral cellular immune response.[438,439,440,441,442,443,444] One review concluded that survival rates at 5 years is

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[431] Younis RT, Hesse SV, Anand VK. Evaluation of the utility and cost-effectiveness of obtaining histopathologic diagnosis on all routine tonsillectomy specimens. *Laryngoscope.* 2001; 111(12): 2166-9.
[432] Syrjanen S. HPV infections and tonsillar carcinoma. *Journal of Clinical Pathology.* 2004; 57(5): 449-55.
[433] Mohammadianpanah M, Omidvai S, Mosalei A et al. Treatment results of tonsillar lymphoma: a 10-year experience. *Annals of Hematology.* 2005; 84(4): 223-6.
[434] Sood S, Nair SB, Fenwick JD et al. Metastatic melanoma of the tonsil. *Journal of Laryngology & Otology.* 1999; 113(11): 1036-8.
[435] Bradford CR, Futran N, Peters G. Management of tonsil cancer. *Head & Neck.* 1999; 21(7): 657-62.
[436] Wang MB, Kuber N, Kerner MM et al. Tonsillar carcinoma: analysis of treatment results. *Journal of Otolaryngology.* 1998; 27(5): 263-9.
[437] Galati LT, Myers EN, Johnson JT. Primary surgery as treatment for early squamous cell carcinoma of the tonsil. *Head & Neck.* 2000; 22(3): 294-6.
[438] Dahlstrand HM, Dalianis T. Presence and influence of human papillomaviruses (HPV) in Tonsillar cancer. *Advances in Cancer Research.* 2005; 93: 59-89.
[439] Li W, Thompson CH, O'Brien CJ et al. Human papillomavirus positivity predicts favourable outcome for squamous carcinoma of the tonsil. *International Journal of Cancer.* 2003; 106(4): 553-8.
[440] Dahlstrand H, Dahlgren L, Lindquist D et al. Presence of human papillomavirus in tonsillar cancer is a favourable prognostic factor for clinical outcome. *Anticancer Research.* 2004; 24(3b): 1829-35.
[441] Dahlgren L, Mellin H, Wangsa D et al. Comparative genomic hybridization analysis of tonsillar cancer reveals a different pattern of genomic imbalances in human papillomavirus-positive and -negative tumors. *International Journal of Cancer.* 2003; 107(2): 244-9.
[442] Mellin H, Friesland S, Auer G et al. Human papillomavirus and DNA ploidy in tonsillar cancer--correlation to prognosis. *Anticancer Research.* 2003; 23(3C): 2821-8.
[443] Friesland S, Mellin H, Munck-Wikland E et al. Human papilloma virus (HPV) and p53 immunostaining in advanced tonsillar carcinoma--relation to radiotherapy response and survival. *Anticancer Research.* 2001; 21(1B): 529-34.

63% in the young adult cohort (20 to 44 years)—where HPV related cancer predominates—compared with 43% for adults over 44 years.[445]

Epidemiology

The annual incidence rate for tonsillar cancer in the US for 1990-1994 was 1.64 per 100,000 men and 0.6 per 100,000 women. This represented a substantial increase compared with 1945-49; in fact, the rate was fully four times higher in women. There has been a recent spike in occurrence among young adults, though some restrict this conclusion to males.[446,447] Such data may be complicated by the changing rates of tonsillectomy. Finland offers data suggesting an increased incidence of cancer of the tonsils between 1956 and 2000—this time clearly applying to both men and women. By 1996-2000, the rates were 0.62 per 100,000 men and 0.18 for women, considerably lower than the US figures but still reflecting the gender imbalance that places men at greater risk.[448]

A total of 57 new cases of tonsillar cancer were reported in B.C. in 2003.

The most frequently reported risk factors for oropharyngeal cancers in general are smoking and alcohol consumption over a prolonged period; the evidence for the role of these factors in tonsillar cancer in particular is still being investigated. The fact that tonsillar cancer rates sometimes have risen as smoking has declined underlines the likelihood of multifactorial causation for the disease; a subset of tonsillar cancer affecting younger patients, sometimes with no history of smoking or alcohol abuse, also suggests another etiological factor.[449,450] The possibility of two separate tumour entities has been reinforced at the molecular level while investigating the most significant causative agency (other than smoking or drinking) examined in recent years, namely, HPV infection.[451,452,453,454,455]

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[444] Schwartz SR, Yueh B, McDougall JK et al. Human papillomavirus infection and survival in oral squamous cell cancer: a population-based study. *Otolaryngology - Head & Neck Surgery.* 2001; 125(1): 1-9.

[445] Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years. *Cancer.* 2005; 103(9): 1843-9.

[446] Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years. *Cancer.* 2005; 103(9): 1843-9.

[447] Frisch M, Hjalgrim H, Jaeger AB et al. Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control.* 2000; 11(6): 489-95.

[448] Syrjanen S. HPV infections and tonsillar carcinoma. *Journal of Clinical Pathology.* 2004; 57(5): 449-55.

[449] El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. *American Journal of Surgical Pathology.* 2003; 27(11): 1463-70.

[450] Klussmann JP, Gultekin E, Weissenborn SJ et al. Expression of p16 protein identifies a distinct entity of tonsillar carcinomas associated with human papillomavirus. *American Journal of Pathology.* 2003; 162(3): 747-53.

[451] Li W, Thompson CH, Xin D et al. Absence of human papillomavirus in tonsillar squamous cell carcinomas from Chinese patients. *American Journal of Pathology.* 2003; 163(6): 2185-9.

[452] Helbig M, Andl T, Kahn T et al. [The role of oncogenic human papillomaviruses in tonsillar squamous cell carcinomas with functional inactivation of the retinoblastoma protein]. *HNO.* 1999; 47(9): 796-803.

[453] Klussmann JP, Weissenborn SJ, Wieland U et al. Human papillomavirus-positive tonsillar carcinomas: a different tumor entity? *Medical Microbiology & Immunology.* 2003; 192(3): 129-32.

Relationship to HPV

Circumstantial evidence for the role of HPV in cancer of the tonsils includes the fact that the risk for this kind of cancer is elevated in people with anogenital carcinomas.[456] Similarly, one study showed that husbands of patients with cervical cancer had an increased risk of tonsillar cancer.[457] Molecular evidence has also been accumulating. HPV was first detected in tonsillar squamous cell carcinoma in 1989. The studies performed between then and 2002 examined over 400 cases of squamous cell carcinoma; a 2004 review of this research reported that HPV DNA was detected 51% of the time. This HPV detection rate is perhaps the highest for any HPV-related malignancy outside of the genital region, suggesting that the tonsils represent a "hot spot for viral transformation."[458,459]

The viral type seen most frequently is HPV 16; the complete breakdown for HPV types in the 2004 analysis mentioned above is shown in the following table (note that some cases involved multiple HPV types).[460]

HPV type	*Percentage of total HPV positive cases*
16	84%
16 / 18	3
6 / 11	3
16 / 33	1.4
31	2.8
33	4.6
Unknown	6

The most recent research, sometimes using more sensitive detection methods, has only strengthened these results. For example, HPV 16 was detected in all 8 tonsillar carcinomas but in none of the control tonsils examined by Begum et al.[461] Similarly, El-Mofty and colleagues detected HPV in 10 of 11 tonsillar cancers in their study; the specific type was HPV 16 in all but one case.[462] A large 2004 study found HPV in

[454] Klussmann JP, Gultekin E, Weissenborn SJ et al. Expression of p16 protein identifies a distinct entity of tonsillar carcinomas associated with human papillomavirus. *American Journal of Pathology.* 2003; 162(3): 747-53.

[455] Li W, Thompson CH, Cossart YE et al. The expression of key cell cycle markers and presence of human papillomavirus in squamous cell carcinoma of the tonsil. *Head & Neck.* 2004; 26(1): 1-9.

[456] Frisch M, Biggar RJ. Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas. *The Lancet.* 1999; 354(9188): 1442-3.

[457] Hemminki K, Dong C, Frisch M. Tonsillar and other upper aerodigestive tract cancers among cervical cancer patients and their husbands. *European Journal of Cancer Prevention.* 2000; 9(6): 433-7.

[458] Venuti A, Badaracco G, Rizzo C et al. Presence of HPV in head and neck tumours: high prevalence in tonsillar localization. *Journal of Experimental & Clinical Cancer Research.* 2004; 23(4): 561-6.

[459] Puscas L. The role of human papilloma virus infection in the etiology of oropharyngeal carcinoma. *Current Opinion in Otolaryngology & Head and Neck Surgery.* 2005; 13(4): 212-6.

[460] Syrjanen S. HPV infections and tonsillar carcinoma. *Journal of Clinical Pathology.* 2004; 57(5): 449-55.

[461] Begum S, Cao D, Gillison M et al. Tissue distribution of human papillomavirus 16 DNA integration in patients with tonsillar carcinoma. *Clinical Cancer Research.* 2005; 11(16): 5694-9.

[462] El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. *American Journal of Surgical Pathology.* 2003; 27(11): 1463-70.

42% of 50 tumours, again type 16 in all but one case.[463] A smaller 2004 study showed HPV positivity of 75% over 8 cases,[464] while 31 of 67 cancers (46%) in a 2003 project were HPV positive (all but 3, or 90%, with HPV 16).[465] Another 2003 study of tonsillar cancer detected HPV 60% of the time—the majority being HPV 16.[466] Finally, a 2005 analysis put the HPV rate at 58%, with HPV 16 detected in 84% of the HPV positive cases.[467] The weight of evidence prompted a 2005 review to conclude that "therapeutic and preventive HPV 16 antiviral immune vaccination trials may be worthwhile, not only in cervical cancer, but also in tonsillar cancer."[468]

Sinonasal Cancers

Description

Malignancies of the sinonasal region are rare; in total, they account for only 3% of head and neck cancers.[469] This part of the body is macro- and micro-anatomically complex; hence tumours localized in the nose demonstrate a remarkable histological diversity.[470,471] At the gross level, subsites such as the nasal vestibule (nearest the nares), the nasal cavity proper, and the paranasal sinuses are distinguished by oncologists, but for the most part the unique features attached to each area will be beyond the scope of our review.[472,473,474,475]

Squamous cell carcinoma dominates (40 to 50% of cases), with adenocarcinoma and adenoid cystic carcinoma constituting the next most frequent varieties of sinonasal cancer (perhaps 1 out of 10 cases).[476] The range of rarer malignancies includes

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[463] Li W, Thompson CH, Cossart YE et al. The expression of key cell cycle markers and presence of human papillomavirus in squamous cell carcinoma of the tonsil. *Head & Neck.* 2004; 26(1): 1-9.
[464] Venuti A, Badaracco G, Rizzo C et al. Presence of HPV in head and neck tumours: high prevalence in tonsillar localization. *Journal of Experimental & Clinical Cancer Research.* 2004; 23(4): 561-6.
[465] Li W, Thompson CH, O'Brien CJ et al. Human papillomavirus positivity predicts favourable outcome for squamous carcinoma of the tonsil. *International Journal of Cancer.* 2003; 106(4): 553-8.
[466] Dahlgren L, Mellin H, Wangsa D et al. Comparative genomic hybridization analysis of tonsillar cancer reveals a different pattern of genomic imbalances in human papillomavirus-positive and -negative tumors. *International Journal of Cancer.* 2003; 107(2): 244-9.
[467] Wittekindt C, Gultekin E, Weissenborn SJ et al. Expression of p16 protein is associated with human papillomavirus status in tonsillar carcinomas and has implications on survival. *Advances in Otorhinolaryngology.* 2005; 62: 72-80.
[468] Dahlstrand HM, Dalianis T. Presence and influence of human papillomaviruses (HPV) in Tonsillar cancer. *Advances in Cancer Research.* 2005; 93: 59-89.
[469] Dulguerov P, Jacobsen MS, Allal AS et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001; 92(12): 3012-29.
[470] Gotte K, Hormann K. Sinonasal malignancy: what's new? *ORL Journal of Otorhinolaryngology & its Related Specialties.* 2004; 66(2): 85-97.
[471] Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *Journal of Clinical Virology.* 2005; 32 Suppl 1: S59-66.
[472] Samaha M, Yoskovitch A, Hier MP et al. Squamous cell carcinoma of the nasal vestibule. *Journal of Otolaryngology.* 2000; 29(2): 98-101.
[473] Bhattacharyya N. Cancer of the nasal cavity: survival and factors influencing prognosis. *Archives of Otolaryngology -- Head & Neck Surgery.* 2002; 128(9): 1079-83.
[474] Blanco AI, Chao KS, Ozyigit G et al. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(1): 51-8.
[475] DeMonte F, Ginsberg LE, Clayman GL. Primary malignant tumors of the sphenoidal sinus. *Neurosurgery.* 2000; 46(5): 1084-91; discussion 91-2.
[476] Grau C, Jakobsen MH, Harbo G et al. Sino-nasal cancer in Denmark 1982-1991--a nationwide survey. *Acta Oncologica.* 2001; 40(1): 19-23.

lymphoma, melanoma, esthesioneuroblastoma, and chondrosarcoma (e.g., in the nasal septum).[477,478,479,480,481]

Treatment protocols vary somewhat with the type and stage of cancer. A combination of surgical excision and radiotherapy is the most common approach, but the surgeon and oncologist often face challenges because of the proximity of the lesions to the eye, brain and cranial nerves.[482] Hence, treatments are associated with numerous complications (such as blindness)[483] and otherwise suboptimal outcomes.[484]

In Canada, the incidence of nasal cancer has been stable, but there was evidence of a drop in mortality rates between 1970 and 1984.[485] A 2001 meta-analysis of the literature from various countries confirmed this trend of improved treatment outcomes into the 1990s. The 5 year survival observed in that review in the most recent decade varied from 94% (stage I tumour) to 27% (stage IV).[486] A 2002 study derived an overall 5-year survival rate of 50% for this type of cancer, consistent with general US data.[487,488] The comparable Finnish figure reported for 1999-2001 was 42%.[489]

Epidemiology

Data specific to nasal and paranasal neoplasia sometimes need to be abstracted from the many general reviews of head and neck cancer in the literature. Some focused statistical studies have been pursued, for example, in Scandinavia. The age-adjusted incidence for nasal cancer is 0.4 per 100,000 males and 0.2 per 100,000 females in Sweden and Finland; the rates are somewhat higher in Denmark, but the male

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[477] Vidal RW, Devaney K, Ferlito A et al. Sinonasal malignant lymphomas: a distinct clinicopathological category. *Annals of Otology, Rhinology & Laryngology.* 1999; 108(4): 411-9.
[478] Brandwein MS, Rothstein A, Lawson W et al. Sinonasal melanoma. A clinicopathologic study of 25 cases and literature meta-analysis. *Archives of Otolaryngology -- Head & Neck Surgery.* 1997; 123(3): 290-6.
[479] Bridger AG, Smee D, Baldwin MA et al. Experience with mucosal melanoma of the nose and paranasal sinuses. *ANZ Journal of Surgery.* 2005; 75(4): 192-7.
[480] Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncology.* 2001; 2(11): 683-90.
[481] Meric F, Osma U, Cureoglu S et al. Chondrosarcoma of the nasal septum. *Rhinology.* 2000; 38(1): 45-7.
[482] Day TA, Beas RA, Schlosser RJ et al. Management of paranasal sinus malignancy. *Current Treatment Options in Oncology.* 2005; 6(1): 3-18.
[483] Dulguerov P, Jacobsen MS, Allal AS et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001; 92(12): 3012-29.
[484] Blanco AI, Chao KS, Ozyigit G et al. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(1): 51-8.
[485] Ayiomamitis A, Parker L, Havas T. The epidemiology of malignant neoplasms of the nasal cavities, the paranasal sinuses and the middle ear in Canada. *Archives of Otorhinolaryngology.* 1988; 244(6): 367-71.
[486] Dulguerov P, Jacobsen MS, Allal AS et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001; 92(12): 3012-29.
[487] Katz TS, Mendenhall WM, Morris CG et al. Malignant tumors of the nasal cavity and paranasal sinuses. *Head & Neck.* 2002; 24(9): 821-9.
[488] Caplan LS, Hall HI, Levine RS et al. Preventable risk factors for nasal cancer. *Annals of Epidemiology.* 2000; 10(3): 186-91.
[489] Storm H, Engholm G, Ferlay J et al. Cancer incidence and mortality in the Nordic countries. Danish Cancer Society, 2003.

preponderance still pertains.[490] Globally, the annual incidence is usually reported as 0.5 to 1.0 per 100,000.[491,492] The highest rates in the world are seen in Japanese males, about 2.5 per 100,000.[493]

Again, research in Scandinavia based on a very large data set confirmed what has been seen elsewhere, namely, that certain occupations are risk factors for sinonasal cancers.[494,495,496] Sometimes the cancers involved are very specific. For instance, the risk of working with leather or wood seems to be localized in the ethmoid sinus and related to adenocarcinoma in particular.[497,498] Similarly, exposure to formaldehyde has been linked to adenocarcinoma rather than squamous cell carcinoma.[499] Smoking, on the other hand, seems to be targeted at squamous cell carcinoma, though the evidence for this risk factor has been mixed.[500,501] One study reported that men who smoked cigarettes had more than a threefold increased risk of nasal cancer.[502]

Relationship to HPV

There are many parallels between sinonasal squamous cell carcinoma and HPV-related lesions at other mucosal sites.[503] Further, recent research has confirmed the actual expression of HPV transforming oncogenes in originally benign tumours in the nose.[504] A review combined several studies to report that HPV was detected in 70 out of 322 (i.e., 21.7% of the total) sinonasal carcinomas analyzed up to 2001. Types 16 or 18 (or both) were found in 80% of the HPV positive cases.[505] A careful study

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[490] Storm H, Engholm G, Ferlay J et al. Cancer incidence and mortality in the Nordic countries. Danish Cancer Society, 2003.

[491] Dulguerov P, Jacobsen MS, Allal AS et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001; 92(12): 3012-29.

[492] Ayiomamitis A, Parker L, Havas T. The epidemiology of malignant neoplasms of the nasal cavities, the paranasal sinuses and the middle ear in Canada. *Archives of Otorhinolaryngology.* 1988; 244(6): 367-71.

[493] Muir CS, Nectoux J. Descriptive epidemiology of malignant neoplasms of nose, nasal cavities, middle ear and accessory sinuses. *Clinical Otolaryngology & Allied Sciences.* 1980; 5(3): 195-211.

[494] Andersen A, Barlow L, Engeland A et al. Work-related cancer in the Nordic countries. *Scandinavian Journal of Work, Environment & Health.* 1999; 25 Suppl 2: 1-116.

[495] Blanco AI, Chao KS, Ozyigit G et al. Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(1): 51-8.

[496] Caplan LS, Hall HI, Levine RS et al. Preventable risk factors for nasal cancer. *Annals of Epidemiology.* 2000; 10(3): 186-91.

[497] Bimbi G, Saraceno MS, Riccio S et al. Adenocarcinoma of ethmoid sinus: an occupational disease. *Acta Otorhinolaryngologica Italica.* 2004; 24(4): 199-203.

[498] t Mannetje A, Kogevinas M, Luce D et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. *American Journal of Industrial Medicine.* 1999; 36(1): 101-7.

[499] Luce D, Gerin M, Leclerc A et al. Sinonasal cancer and occupational exposure to formaldehyde and other substances. *International Journal of Cancer.* 1993; 53(2): 224-31.

[500] t Mannetje A, Kogevinas M, Luce D et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. *American Journal of Industrial Medicine.* 1999; 36(1): 101-7.

[501] Talmi YP, Wolf M, Horowitz Z et al. Smoking-induced squamous-cell cancer of the nose. *Archives of Environmental Health.* 2002; 57(5): 422-4.

[502] Caplan LS, Hall HI, Levine RS et al. Preventable risk factors for nasal cancer. *Annals of Epidemiology.* 2000; 10(3): 186-91.

[503] Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *Journal of Clinical Virology.* 2005; 32 Suppl 1: S59-66.

[504] Harris MO, Beck JC, Lancaster W et al. The HPV 6 E6/E7 transforming genes are expressed in inverted papilloma. *Otolaryngology -- Head & Neck Surgery.* 1998; 118(3 Pt 1): 312-8.

[505] Syrjanen KJ. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.

published in 2005 confirmed a 20% HPV detection rate among sinonasal squamous cell carcinomas—type 16 in each case. No HPV DNA was detected in clinically intact mucosa or in nasal polyps.[506]

Cancer of the Ocular Surface

Description
Tumours of the ocular surface comprise a wide spectrum of conditions, both benign and malignant; the latter includes aggressive and even life-threatening forms such as melanoma and Kaposi's sarcoma.[507] In particular for our focus, various squamous cell cancers of the cornea and conjunctiva exist, ranging from intraepithelial neoplasia to invasive tumours.[508] Management, which varies with the extent of the lesion, can include various kinds of ablative and topical therapy.

Epidemiology
Ocular squamous cell carcinoma is very rare; in fact, it is only the third most common eye tumour (after melanoma and lymphoma).[509] A US study estimated an annual incidence of only 0.03 per 100,000.[510] The long held understanding is that exposure to ultraviolet (UV) radiation is a major etiologic factor in the development of ocular surface malignancy. Recent theories suggest that HPV (see below) needs UV as a co-factor in order for cancer to develop. "Sun-friendly" areas in fact show a higher incidence of ocular surface squamous cell carcoinoma; Australia, for example, has reported a rate of 1.9 per 100,000, sixty times higher than the US incidence.[511]

Relationship to HPV
The evidence for an etiological link between ocular surface squamous cell carcinoma and HPV is still being developed. Sometimes results have appeared at best mixed or modest.[512,513] While HPV may be detected in over 50% or more of lesions of the external eye, it also is found in apparently healthy ocular surfaces.[514,515] A recent small study was more compelling, finding HPV 16 or 18 in *all* cases of conjunctival intraepithelial neoplasia examined.[516] The suspected dominance of HPV 16 and 18 in

[506] Hoffmann M, Klose N, Gottschlich S et al. Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. *Cancer Letters.* 2005; Epublished ahead of print: 1-7.
[507] Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Survey of Ophthalmology.* 2004; 49(1): 3-24.
[508] Basti S, Macsai MS. Ocular surface squamous neoplasia: a review. *Cornea.* 2003; 22(7): 687-704.
[509] Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Survey of Ophthalmology.* 1995; 39(6): 429-50.
[510] Sun EC, Fears TR, Goedert JJ. Epidemiology of squamous cell conjunctival cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 1997; 6(2): 73-7.
[511] Basti S, Macsai MS. Ocular surface squamous neoplasia: a review. *Cornea.* 2003; 22(7): 687-704.
[512] Toth J, Karcioglu ZA, Moshfeghi AA et al. The relationship between human papillomavirus and p53 gene in conjunctival squamous cell carcinoma. *Cornea.* 2000; 19(2): 159-62.
[513] Basti S, Macsai MS. Ocular surface squamous neoplasia: a review. *Cornea.* 2003; 22(7): 687-704.
[514] Karcioglu ZA, Issa TM. Human papilloma virus in neoplastic and non-neoplastic conditions of the external eye. *British Journal of Ophthalmology.* 1997; 81(7): 595-8.
[515] Nakamura Y, Mashima Y, Kameyama K et al. Detection of human papillomavirus infection in squamous tumours of the conjunctiva and lacrimal sac by immunohistochemistry, in situ hybridisation, and polymerase chain reaction. *British Journal of Ophthalmology.* 1997; 81(4): 308-13.
[516] Scott IU, Karp CL, Nuovo GJ. Human papillomavirus 16 and 18 expression in conjunctival intraepithelial neoplasia. *Ophthalmology.* 2002; 109(3): 542-7.

squamous cell carcinogenesis at the ocular surface is confirmed in earlier studies;[517] however, some other types of HPV (notably related to the disease known as epidermodysplasia verruciformis) have also been implicated.[518]

The role of HPV in the development of other rare cancers of the eye, including retinoblastoma, is also being investigated.[519]

Other Head and Neck Cancers

The pharynx is commonly known as the throat (especially if the larynx is included). Situated at the front of the upper neck, it is essentially the region where the digestive tract and respiratory tract cross. In addition to the oropharynx (see above under oral cancers), there are two other subdivisions: the nasopharynx, adjacent to the posterior part of the nasal cavity, and the hypopharynx, or the lower part leading to the larynx and the esophagus (the alternate term "laryngopharynx" seems to be synonymous with hypopharynx, though it can possibly be used to distinguish that part of the lower pharynx which extends anteriorly to the epiglottis and which is adjacent to or, by some definitions, even includes the larynx). It is easy to see that terms such as pharyngeal and laryngeal cancer can suffer from a large degree of overlap. The confusion in terminology arises because of a shifting emphasis, i.e., deciding whether the pharynx properly belongs to the digestive tract or the respiratory tract. Thus, the hypopharynx is considered by the American Cancer Society to be that part of the esophagus which basically surrounds the larynx.

This brief anatomical review reveals some additional categories of cancer which are emerging as possibly being HPV related. These include hypopharyngeal, esophageal, nasopharyngeal, and even tracheal and bronchial neoplasia (though the latter two sites more often are considered cancers of the upper aerodigestive tract rather than of the head and neck per se).

Although lying outside the scope of our report, it is significant to note the accumulating data which makes a subset of the malignancies in these various areas a potential part of the HPV vaccination story.

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[517] Nakamura Y, Mashima Y, Kameyama K et al. Detection of human papillomavirus infection in squamous tumours of the conjunctiva and lacrimal sac by immunohistochemistry, in situ hybridisation, and polymerase chain reaction. *British Journal of Ophthalmology.* 1997; 81(4): 308-13.

[518] Ateenyi-Agaba C, Weiderpass E, Smet A et al. Epidermodysplasia verruciformis human papillomavirus types and carcinoma of the conjunctiva: a pilot study. *British Journal of Cancer.* 2004; 90(9): 1777-9.

[519] Palazzi MA, Yunes JA, Cardinalli IA et al. Detection of oncogenic human papillomavirus in sporadic retinoblastoma. *Acta Ophthalmologica Scandinavica.* 2003; 81(4): 396-8.

Other Cancer Types

Given the extensive range of cancers and sites in which HPV has been detected, it would be a fair question to ask what the virus is *not* involved with, especially in reference to the epithelial and mucosal tissues for which it seems to have a great affinity. Indeed, the "HPV circle" seems to only be getting wider, increasing the potential efficacy of any vaccination program. Notably, skin malignancies have been receiving a lot of attention. A broad spectrum of HPV types (including 16) has been detected in the skin of patients with non-melanoma skin cancers,[520,521] which may be very significant given the high incidence of such diseases (100 to 150 per 100,000 Caucasians).[522]

Another very significant cancer site, the lung and related passageways, has been pulled into the story. One 2002 review of studies up to that point noted that HPV DNA had been detected in 2,468 cases of bronchial carcinomas.[523] Recently, HPV has also been implicated in pulmonary adenocarcinoma.[524]

Finally, we can mention the recent suggestion (contrary to earlier scepticism), that HPV may play a role in bladder cancer.[525,526] The first international report of a bladder wart testing positive for HPV 16 and 18 DNA is certain to add fuel to the discussion.[527]

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[520] Forslund O, Ly H, Reid C et al. A broad spectrum of human papillomavirus types is present in the skin of Australian patients with non-melanoma skin cancers and solar keratosis. *British Journal of Dermatology.* 2003; 149(1): 64-73.

[521] Iftner A, Klug SJ, Garbe C et al. The prevalence of human papillomavirus genotypes in nonmelanoma skin cancers of nonimmunosuppressed individuals identifies high-risk genital types as possible risk factors. *Cancer Research.* 2003; 63(21): 7515-9.

[522] Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *New England Journal of Medicine.* 2001; 344(13): 975-83.

[523] Syrjanen KJ. HPV infections and lung cancer. *Journal of Clinical Pathology.* 2002; 55(12): 885-91.

[524] Chen YC, Chen JH, Richard K et al. Lung adenocarcinoma and human papillomavirus infection. *Cancer.* 2004; 101(6): 1428-36.

[525] Khaled HM, Bahnassi AA, Zekri AR et al. Correlation between p53 mutations and HPV in bilharzial bladder cancer. *Urologic Oncology.* 2003; 21(5): 334-41.

[526] Griffiths TR, Mellon JK. Human papillomavirus and urological tumours: II. Role in bladder, prostate, renal and testicular cancer. *British Journal of Urology International.* 2000; 85(2): 211-7.

[527] Chrisofos M, Skolarikos A, Lazaris A et al. HPV 16/18-associated condyloma acuminatum of the urinary bladder: first international report and review of literature. *International Journal of STD and AIDS.* 2004; 15(12): 836-8.

Non-malignant Diseases

Genital Warts

Description
Genital warts, also known as venereal warts or condylomata acuminata, are a benign form of papilloma. They often present "exophytically," that is, an outward growth consisting of a central core of connective tissue covered by epithelium; however, the majority of such warts in the anogenital region seem to be so-called flat condylomata.[528] As the name suggests, they usually occur on the mucous membrane or skin of the external genitals or the perianal region. This localization explains the use of specific alternate terms such as "external" or "visible" genital warts and the broader collective category "anogenital warts" (which usually also refers to external areas only). However, internal genital warts, e.g., of the cervix, also occur.[529] The mucous membranes of the urethra, vagina, anus and oropharynx (including the tonsils) are other locations where internal warts can be found.[530,531,532,533,534]

Although the main focus of this section is external genital warts, there is an overlap between the two types. One common feature is the role of sexual behaviour as a risk factor (see below). For example, intra-anal warts are found primarily in individuals who have had receptive anal intercourse.[535] One study showed that 78% of patients with external anal warts had internal lesions as well.[536]

External genital warts can be located on the penis, vulva, scrotum, perineum, and perianal skin. They are flesh-coloured lesions which range from small bumps to flat, verrucous, or pedunculated (stalked) forms.[537] Warts, dysplasia, and cancer in the anogenital region are all epithelial lesions that can be difficult to distinguish from one another.[538]

People with genital warts report a reduced quality of life and curtailed daily activities, especially in terms of the discomfort attached to having or to treating the

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[528] Handsfield HH. Clinical presentation and natural course of anogenital warts. *American Journal of Medicine.* 1997; 102(5A): 16-20.
[529] Brisson J, Roy M, Fortier M et al. Condyloma and intraepithelial neoplasia of the uterine cervix: a case-control study. *American Journal of Epidemiology.* 1988; 128(2): 337-42.
[530] Zaak D, Hofstetter A, Frimberger D et al. Recurrence of condylomata acuminata of the urethra after conventional and fluorescence-controlled Nd:YAG laser treatment. *Urology.* 2003; 61(5): 1011-5.
[531] Tsuji K, Nakamura Y, Mori I et al. [Human papilloma virus infection in vaginal condyloma acuminatum]. *Japanese Journal of Clinocal Pathology.* 2003; 51(2): 93-7.
[532] Vukasin P. Anal condyloma and HIV-associated anal disease. *Surgical Clinics of North America.* 2002; 82(6): 1199-211, vi.
[533] Zunt SL, Tomich CE. Oral condyloma acuminatum. *Journal of Dermatology & Surgical Oncology.* 1989; 15(6): 591-4.
[534] Tominaga S, Fukushima K, Nishizaki K et al. Presence of human papillomavirus type 6f in tonsillar condyloma acuminatum and clinically normal tonsillar mucosa. *Japanese Journal of Clinocal Oncology.* 1996; 26(6): 393-7.
[535] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.
[536] Vukasin P. Anal condyloma and HIV-associated anal disease. *Surgical Clinics of North America.* 2002; 82(6): 1199-211, vi.
[537] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.
[538] Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. *American Journal of Obstetrics & Gynecology.* 2003; 189(3 Suppl): S3-11.

warts.[539] The health care system also bears a burden. In the UK, for instance, external genital warts are among the most commonly treated sexually transmitted disease, accounting for 22% of visits to sexual health clinics or genitourinary medical practices.[540]

Management of external genital warts involves applying a topical chemical, ablative therapy (e.g., laser, surgery), or a combination of the two approaches. Eradication is achieved in 20 to 90% of cases, depending on the method. For instance, the topical agent known as imiquimod has been used since 1997; it has a clearance rate of 30 to 50%, limited side effects and a low recurrence rate.[541] If a patient is not immuno-compromised, genital warts may even spontaneously diminish or resolve without treatment; however, HPV can persist in the normal epithelium, creating a risk of disease recurrence.[542,543] For example, a 2003 UK study in the UK that compared topical treatments found a 12 week recurrence rate of 43% of all initially cleared subjects.[544]

Epidemiology

The annual incidence of genital warts in the US has been estimated to be 1.4 to 2.4 per 1,000.[545, 546] Among the 500,000 to 1 million new cases that occur each year in the US, the distribution between men and women is virtually equal.[547]

The most noted demographic risk factor is age. The cohort between the ages of 20 and 29 years is most at risk for a new diagnosis of external genital warts, as indicated on the following table.[548,549]

[539] Badia X, Colombo JA, Lara N et al. Combination of qualitative and quantitative methods for developing a new Health Related Quality of Life measure for patients with anogenital warts. *Health & Quality of Life Outcomes.* 2005; 3(1): 24.
[540] Hughes G, Simms I, Rogers PA et al. New cases seen at genitourinary medicine clinics: England 1997. *Commun Dis Rep CDR Suppl.* 1998; 8(7): S1-11.
[541] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.
[542] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[543] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.
[544] Lacey CJ, Goodall RL, Tennvall GR et al. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sexually Transmitted Diseases.* 2003; 79(4): 270-5.
[545] Stanley M. Chapter 17: Genital human papillomavirus infections--current and prospective therapies. *Journal of the National Cancer Institute Monograph.* 2003; (31): 117-24.
[546] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clinical Infectious Diseases.* 2003; 36(11): 1397-403.
[547] Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *American Journal of Medicine.* 1997; 102(5A): 28-37.
[548] Fleischer AB, Jr., Parrish CA, Glenn R et al. Condylomata acuminata (genital warts): patient demographics and treating physicians. *Sexually Transmitted Diseases.* 2001; 28(11): 643-7.
[549] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clinical Infectious Diseases.* 2003; 36(11): 1397-403.

Genital Wart Prevalence in the United States Based on Care Provided by Private Health Plans Rate per 1,000 Person Years		
Age Group	**Genital Warts** Males	Females
0-4	0.13	0.07
5-9	0.34	0.25
10-14	0.41	0.43
15-19	0.65	2.87
20-24	2.93	6.20
25-29	5.01	3.94
30-34	3.88	2.65
35-39	2.52	1.99
40-44	1.89	1.39
45-49	1.28	1.44
50-54	1.18	0.92
55-59	0.86	0.86
60-64	1.00	0.76
65+	0.87	0.55
Total	**1.67**	**1.65**

The strongest behavioural risk factors involve sexual practices. This is consistent with the fact that HPV infection is spread primarily through vaginal, anal or oral sex. The trend in recent decades towards the onset of HPV-related infections at a younger age is considered to reflect the younger age of first sexual intercourse. Other well-known risk factors include multiple sexual partners and oral contraceptive use.[550] Perinanal warts are common in men who practice receptive anal intercourse.[551]

Genital warts are highly contagious; it is estimated that 66% of individuals having sexual contact with an infected partner will develop genital warts within three months.[552] Canadian estimates indicate that 2% of sexually active young women have genital warts,[553] whereas US data suggest a 0.5% to 1% prevalence among sexually active young adults.[554,555]

[550] Fleischer AB, Jr., Parrish CA, Glenn R et al. Condylomata acuminata (genital warts): patient demographics and treating physicians. *Sexually Transmitted Diseases.* 2001; 28(11): 643-7.
[551] Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. *Medical Microbiology and Immunology (Berl).* 2004; 193(1): 35-44.
[552] The Society of Obstetricians and Gynaecologists of Canada. *Human Papillomavirus: the most common sexually transmitted disease.* No date. Available at http://www.sogc.org/sogcnet/sogc%5Fdocs/press/releases2005/documents/finalenglishprimerapril18.pdf. Accessed September 2005.
[553] The Society of Obstetricians and Gynaecologists of Canada. *Human Papillomavirus: the most common sexually transmitted disease.* No date. Available at http://www.sogc.org/sogcnet/sogc%5Fdocs/press/releases2005/documents/finalenglishprimerapril18.pdf. Accessed September 2005.
[554] Fleischer AB, Jr., Parrish CA, Glenn R et al. Condylomata acuminata (genital warts): patient demographics and treating physicians. *Sexually Transmitted Diseases.* 2001; 28(11): 643-7.
[555] Koutsky L. Epidemiology of genital human papillomavirus infection. *American Journal of Medicine.* 1997; 102(5A): 3-8.

In patients where the immune system is compromised (i.e., in the case of HIV infection or organ transplantation) genital warts are more prevalent.[556] In a study comparing HIV-1 positive and HIV-1 negative women, those with HIV were at least 7 times more likely to have genital warts or neoplasia in the vulva or vaginal region.[557]

Relationship to HPV

HPV infection manifests itself most frequently in the form of genital warts. Evidence suggests that more than 80 to 90% of genital warts result from HPV types 6 and 11, usually with type 6 predominating.[558,559] Lesions demonstrating only low-risk HPV DNA are considered unlikely to lead to cancer.[560] Conversely, HPV types 16,18,31,33,and 35 have been found in genital warts that progressed to neoplasia, with types 16 and 18 having the highest maliganancy potential.[561,562] Co-infection with HPV 6 or 11 and a higher risk type of the virus in fact has been detected in up to 44% of cases of genital warts.[563,564] This suggests that a bivalent vaccine addressing HPV 16 and 18, while not dealing with genital warts per se may have some impact on carcinogenic transformation of such lesions.

Recurrent Respiratory Papillomatosis

Description

Recurrent respiratory papillomatosis (RRP), a benign neoplasm notable for its juvenile presentation, diminishes the diameter of the child's airway, leading to obstructed breathing. Most often this type of lesion is found in the larynx; less commonly, papillomas are found in the trachea, esophagus, lungs, parenchyma, oropharnx, oral cavity, nasal cavity, and other head and neck sites.[565] There is significant physical and emotional burden for those affected by RPP, as well as the cost of ongoing invasive treatments; none of the therapies have been found to be curative, which accounts for the characterization of "recurrent."

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[556] Silverberg MJ, Ahdieh L, Munoz A et al. The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. *Sexually Transmitted Diseases.* 2002; 29(8): 427-35.

[557]Conley LJ, Ellerbrock TV, Bush TJ et al. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. *The Lancet.* 2002; 359(9301): 108-13.

[558] Skerlev M, Grce M, Sirotkoviae-Skerlev M et al. Human papillomavirus male genital infections: clinical variations and the significance of DNA typing. *Clinical Dermatology.* 2002; 20(2): 173-8.

[559] Grce M, Husnjak K, Skerlev M et al. Detection and typing of human papillomaviruses by means of polymerase chain reaction and fragment length polymorphism in male genital lesions. *Anticancer Research.* 2000; 20(3B): 2097-102.

[560] Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. *American Journal of Obstetrics & Gynecology.* 2003; 189(3 Suppl): S3-11.

[561] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.

[562] Skerlev M, Grce M, Sirotkoviae-Skerlev M et al. Human papillomavirus male genital infections: clinical variations and the significance of DNA typing. *Clinical Dermatology.* 2002; 20(2): 173-8.

[563] Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. *Medical Microbiology and Immunology (Berl).* 2004; 193(1): 35-44.

[564] Tsuji K, Nakamura Y, Mori I et al. [Human papilloma virus infection in vaginal condyloma acuminatum]. *Japanese Journal of Clinocal Pathology.* 2003; 51(2): 93-7.

[565] Wiatrak BJ. Overview of recurrent respiratory papillomatosis. *Current Opinion in Otolaryngology & Head and Neck Surgery.* 2003; 11(6): 433-41.

Epidemiology
The most severe cases are in children under the age of four. Often they must submit to as many as four surgeries a year. The number of new diagnoses of RRP peaks again between the ages of 20 and 30. The incidence in the United States has been estimated at between 0.36 and 1.11 per 100,000 children under the age of 18. The prevalence is estimated at between 1.69 and 2.59 per 100,000 children.[566] Incidence rates in adults are uncertain but have been estimated at 1.8 per 100,000 adults. [567]

Potential causes include peripartum transmission of the virus from infected mothers, transmission through sexual abuse in older children and transmission through oroanal or orogenital contact in adults.

Relationship to HPV
For nearly 50 years, research has identified HPV as the cause of RRP. Much research has focused on the vertical transmission of HPV from an infected mother; an uncommon but serious consequence of such transmission is neonatal laryngeal papillomatosis.[568] Shykhon et al. found that, of the 30-50% of children born to mothers testing positive for HPV DNA, 1 in 400 were likely to develop RRP.[569] In a 2005 study, HPV was found in 80% of RRP cases, mostly types 6 and 11.[570]

Sinonasal Papilloma

Description
The research on sinonasal papillomas has highlighted three specific types of benign lesions: squamous cell papilloma, inverted (Schneiderian) papilloma, and cylindic (columnar) papilloma.[571,572] However, the delineation of these classifications is inconsistent in the literature, which complicates identifying HPV association with particular sinonasal papillomas.[573] All 3 types of papillomas have a tendency to recur and progress after surgery, but it is the inverted type which appears to be most

[566] Armstrong L, Preston E, Reichert M, et al. Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle. *Clinical Infectious Diseases.* 2000; 31(1): 107-9.
[567] Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clinical Otolaryngology and Allied Sciences.* 2002; 27(4): 237-43.
[568] Handsfield HH. Clinical presentation and natural course of anogenital warts. *American Journal of Medicine.* 1997; 102(5A): 16-20.
[569] Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clinical Otolaryngology and Allied Sciences.* 2002; 27(4): 237-43.
[570] Szeps M, Dahlgren L, Aaltonen LM et al. Human papillomavirus, viral load and proliferation rate in recurrent respiratory papillomatosis in response to alpha interferon treatment. *Journal of General Virology.* 2005; 86(Pt 6): 1695-702.
[571] Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *Journal of Clinical Virology.* 2005; 32 Suppl 1: S59-66.
[572] Buchwald C, Lindeberg H, Pedersen BL et al. Human papilloma virus and p53 expression in carcinomas associated with sinonasal papillomas: a Danish Epidemiological study 1980-1998. *Laryngoscope.* 2001; 111(6): 1104-10.
[573] Batsakis JG, Suarez P. Schneiderian papillomas and carcinomas: a review. *Advances on Anatomic Pathology.* 2001; 8(2): 53-64.

associated with malignancy. According to one Danish study, the transformation of papillomas of all types accounts for about 15% of sinonasal carcinomas.[574]

Epidemiology
Sinonasal papillomas are rare, showing an incidence of 0.6 per 100,000 worldwide. The male to female ratio is 3:1.[575] They occur within a wide age range which spans 5 decades.[576] Significant risk factors for the disease include smoking and the use of alcohol.

Relationship to HPV
The evidence supports the idea that sinonasal papillomas are similar to other benign HPV-related lesions which favour a viral cause.[577] Syrjanen found a third of sinonasal tumors to be HPV positive in a combined group of 1,041 from several studies.[578]

HPV infection appears to be higher in inverted papillomas, but the evidence has been mixed.[579,580] One study demonstrated HPV in 60 to 70% of inverted papilloma.[581]

The two low-risk HPV types 6 and 11 are consistently the most frequent ones detected in benign sinonasal lesions.[582,583]

Conjunctival Papilloma

Description
The conjunctiva is the mucous membrane lining the visible part of the eye and the eyelid. Conjunctival papillomas are benign tumors that are classified as infectious and noninfectious. The infectious conjunctival papilloma are equivalent to squamous cell papilloma at other sites, that is, related to HPV. Noninfectious conjunctival papillomas are believed to result from UV exposure.

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[574] Buchwald C, Lindeberg H, Pedersen BL et al. Human papilloma virus and p53 expression in carcinomas associated with sinonasal papillomas: a Danish Epidemiological study 1980-1998. *Laryngoscope.* 2001; 111(6): 1104-10.
[575] Syrjanen KJ. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.
[576] Batsakis JG, Suarez P. Schneiderian papillomas and carcinomas: a review. *Advances on Anatomic Pathology.* 2001; 8(2): 53-64.
[577] Syrjanen S. Human papillomavirus (HPV) in head and neck cancer. *Journal of Clinical Virology.* 2005; 32 Suppl 1: S59-66.
[578] Syrjanen KJ. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.
[579] Syrjanen KJ. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.
[580] Buchwald C, Franzmann MB, Jacobsen GK et al. Human papillomavirus (HPV) in sinonasal papillomas: a study of 78 cases using in situ hybridization and polymerase chain reaction. *Laryngoscope.* 1995; 105(1): 66-71.
[581] Wang D, Li Y, Sun K. [Nasal inverted papilloma and human papilloma virus]. *Journal of Clinical Otorhinolaryngology.* 1998; 12(3): 118-9.
[582] Hoffmann M, Klose N, Gottschlich S et al. Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. *Cancer Letters.* 2005; Epublished ahead of print: 1-7.
[583] Syrjanen KJ. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.

Treatment of choice for benign lesions is close observation, followed by surgery in conjunction with medication; direct freezing and laser treatment are also options.[584,585] The recurrence rate is high.[586]

Epidemiology
Conjunctival papillomas are relatively common tumors seen in both children and adults, but the majority of cases cluster at age 20 to 39.[587] Another study looking specifically at children less than 17 years found squamous cell papillomas to be third in frequency for all eyelid tumors in Taiwanese children.[588] In B.C., no new cases were reported in the under 40 age grouping for 1999-2003; a total of 6 new cases were detected in older adults in this 5 year period.

The link between conjunctival papilloma and a deficient immune system, such as is found in HIV positive individuals and organ transplant recipients, has been established; this is consistent with our experience of other HPV-related disease.

Relationship to HPV
HPV types 6 and 11 have been shown to have a strong association with squamous cell papilloma of the conjunctiva,[589] though the evidence is not always supportive of such a conclusion.[590] In several studies before 2001, HPV 6 and / or 11 was detected 50 to 65% of time.[591] Types 16 and 18 have also been isolated in the conjunctiva of the eye.[592] Sjo et al. found HPV 6, 11 or 16 in 92% of the 52 conjunctival papilloma patients they examined. Human papillomavirus has also been found in normal conjunctiva, which leads to the conclusion that the virus requires a co-factor for the development of papilloma.[593]

How HPV actually establishes itself in the eye is not yet fully determined. In the paediatric cases of papilloma, the virus is thought to be transferred to children as they pass through the birth canal of an infected mother.[594] In one report, conjunctival

[584] Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Survey of Ophthalmology.* 2004; 49(1): 3-24.
[585] Morgenstern KE, Givan J, Wiley LA. Long-term administration of topical interferon alfa-2beta in the treatment of conjunctival squamous papilloma. *Archives of Ophthalmology.* 2003; 121(7): 1052-3.
[586] Palazzi MA, Erwenne CM, Villa LL. Detection of human papillomavirus in epithelial lesions of the conjunctiva. *Sao Paulo Medical Journal.* 2000; 118(5): 125-30.
[587] Sjo NC, Heegaard S, Prause JU et al. Human papillomavirus in conjunctival papilloma. *British Journal of Ophthalmology.* 2001; 85(7): 785-7.
[588] Hsu HC, Lin HF. Eyelid tumors in children: a clinicopathologic study of a 10-year review in southern Taiwan. *Ophthalmologica.* 2004; 218(4): 274-7.
[589] McDonnell PJ, McDonnell JM, Kessis T et al. Detection of human papillomavirus type 6/11 DNA in conjunctival papillomas by in situ hybridization with radioactive probes. *Human Pathology.* 1987; 18(11): 1115-9.
[590] Palazzi MA, Erwenne CM, Villa LL. Detection of human papillomavirus in epithelial lesions of the conjunctiva. *Sao Paulo Medical Journal.* 2000; 118(5): 125-30.
[591] Sjo NC, Heegaard S, Prause JU et al. Human papillomavirus in conjunctival papilloma. *British Journal of Ophthalmology.* 2001; 85(7): 785-7.
[592] Karcioglu ZA, Issa TM. Human papilloma virus in neoplastic and non-neoplastic conditions of the external eye. *British Journal of Ophthalmology.* 1997; 81(7): 595-8.
[593] Sjo NC, Heegaard S, Prause JU et al. Human papillomavirus in conjunctival papilloma. *British Journal of Ophthalmology.* 2001; 85(7): 785-7.
[594] McDonnell PJ, McDonnell JM, Kessis T et al. Detection of human papillomavirus type 6/11 DNA in conjunctival papillomas by in situ hybridization with radioactive probes. *Human Pathology.* 1987; 18(11): 1115-9.

papilloma demonstrating HPV types 6 and 11 was diagnosed in a male infant, where the mother was known to have genital warts of the vulva during pregnancy.[595] In adults, the virus is likely spread by direct skin-to-skin contact (e.g., the hand touching the eye).

Other Skin Lesions

In addition to the malignant and non-malignant diseases noted above, HPV also manifests itself in a variety of both common and less common skin lesions. These include common warts (verrucae vulgaris), plantar warts, flat warts (verrucae plana), butcher warts, extragenital Bowen disease, and macular plaques of epidermodysplasia verruciformis.

The incidence of the more common warts (common and plantar warts) is estimated at approximately 10% in the population of 12 to 16 years olds, decreasing thereafter with age.[596] Common warts are caused by HPV types 2 and 4 and occur most often on the hands, fingers or near the fingernails. Plantar warts are benign growths caused by HPV type 1 that occur on the sole, heel or ball of the foot. These warts can occur when HPV accesses the body through tiny cuts or breaks in the skin. Infection with the virus can occur very easily e.g. by touching a towel used by an infected individual. The HPV type 1 virus (causing plantar warts) is most commonly encountered on contaminated surfaces, such as the tile floors of public locker rooms, showers, and swimming pools.

It is clear that common warts are not caused by oncogenic strains of HPV. However, it is very possible that some common warts may be precursors of squamous carcinomas of the skin, as HPV viral DNA can be recovered from some tumour tissue samples.

[595] Egbert JE, Kersten RC. Female genital tract papillomavirus in conjunctival papillomas of infancy. *American Journal of Ophthalmology.* 1997; 123(4): 551-2.
[596] See http://www.stanford.edu/group/virus/papilloma/2004goglincarnevale/Papilloma/HPV1.htm (accessed January 2006).

Summary

Information presented above on the clinical burden of HPV infection is summarized on the following table. This information will be used in estimating the burden of HPV infection in British Columbia as well as the potential impact of a vaccination program.

The Clinical Burden of HPV Infection

	Proportion Due to HPV Infection	HPV Type 16	18	45	31	35	52	68	6	11	2	Reference
Cancers												
Cancer of the Cervix	100%	54.6%	11.0%	4.4%	3.4%	1.4%	2.2%					Munoz (2003)
Ano-genital Cancers												
Cancer of the Vulva	46.0%	96.0%										Ngan (1999)
	64.2%	100.0%										Menczer (2000)
Cancer of the Vagina	64.0%	12.5%	58.3%						8.3%			Daling (2002)
	43.7%	100.0%										Koyamatsu (2003)
Cancer of the Penis	42.0%	60.0%	3.3%	6.6%		5.0%	6.6%	5.0%	8.3%			Rubin (2001)
Cancer of the Anus	87.9%	73.0%	6.9%									Daling (2004)
Head and Neck Cancers												
Cancer of the Larynx	25.0%	Primary										Syrjanen (2005)
Oral Cancers	22.0%	Primary										Syrjanen (2005)
Cancer of the Tonsills	51.0%	84.0%							3.0%			Syrjanen (2005)
Sino-nasal Cancers	21.7%	100.0%										Syrjanen (2005)
												Hoffman (2005)
Cancer of the Ocular Surface	50.0%	100.0%										Nakamura (1997)
Non-malignant Diseases												
Genital Warts	100.0%								90%			Gunter (2003)
Incidence of 2.4 cases per 1,000 population per year												Stanley (2003)
Incidence of 1.57 new claims per 1,000 (1998-2001)												Koshiol (2004)
Equal distribution between men and women												
Recurrent Respiratory Papillomatosis	76.2%								60%	40%		Syrjanen (2005), Major (2005)
Prevalence in children < 18 - 1.69 to 2.59 / 100,000												Armstrong (2000)
Incidence in children < 18 - 0.36 to 1.11 / 100,000												Armstrong (2000)
Incidence in adults - 1.8 per 100,000 (uncertain)												Shykhon (2002)
Sino-nasal Papilloma	33.3%											Syrjanen (2005)
Incidence - 0.6 per 100,000									Primary			Syrjanen (2003)
Male to female ratio of 3:1												
Conjunctival Papilloma	92.0%								85.4%			Sjo (2001)
Incidence rate not known												Duong (2004)

References:

Armstrong LR, Preston EJ, Reichert M, et al. Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle. *Clinical Infectious Diseases* . 2000; 31(1): 107-9.
Daling J, Madeleine M, Schwartz S et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. *Gynecologic Oncology.* 2002; 84(2): 263-70.
Daling J, Madeleine M, Johnson L, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004; 101: 270-80.
Duong H, Copeland R. Papillloma, Conjunctival. *Emedicine* available at www.emedicine.com/oph/topic611 (accessed July 2005)

Gunter J. Genital and perianal warts: New treatment opportunities for human papillomavirus infection. *American Journal of Obstetrics and Gynecology* 2003; 189: S3 - S11.
Hoffmann M, Klose N, Gottschlich S et al. Detection of human papillomavirus DNA in benign and malignant sinonasal neoplasms. *Cancer Letters.* 2005; Epublished ahead of print: 1-7.
Koshiol J, St. Laurant S, Pimenta J. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. *Sexually Transmitted Diseases* 2004; 31(12): 748-52.
Koyamatsu Y, Yokoyama M, Nakao Y, et al. A comparative analysis of human papillomavirus types 16 and 18 and expression of p53 gene and Ki-67 in cervical, vaginal, and vulvar carcinomas. *Gynecologic Oncology* 2003; 90: 547-51.

Major T, Szarka K, Sziklai I, et al. The characteristics of human papillomavirus DNA in head and neck cancers and papillomas. *Journal of Clinical Pathology* 2005; 58: 51-55.
Menczer J, Fintsi Y, Arbel-Alon S, et al. The presence of HPV 16, 18 amd p53 immunohistochemical staining in tumour tissue of Israeli Jewish women with cervical and vulvar neoplasia. *European Journal of Gynaecologic Oncology* 2000; 21(1): 30-4.
Munoz N, Bosch X, Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine* 2003; 348(6): 518-527.
Nakamura Y, Mashima Y, Kameyama K, et al. Detection of human papillomavirus infection in squamous tumours of the conjunctiva and lacrimal sac by immunohistochemistry, in situ hybridisation, and polymerase chain reaction. *British Journal of Ophthalmology* 1997; 81: 308-13.
Ngan H, Cheung A, Liu S, et al. Abnormal expression or mutation of TP53 and HPV in vulvar cancer. *European Journal of Cancer* 1999; 35(3): 481-4.
Rubin M, Kleter B, Zhou M, et al. Detection and typing oof human papillomavirus DNA in penile carcinoma. *American Journal of Pathology* 2001; 159: 1211-18.
Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clinical Otolaryngology* 2002; 27: 237-43.
Sjo N, Heegaard S, Prause J, et al. Human papillomavirus in conjunctival papilloma. *British Journal of Ophthalmology* 2001; 85: 785-7.
Stanley M. Chapter 17: Genital human papillomavirus infections - current and prospective therapies. *Journal of the National Cancer Institute Monographs* 2003; 31: 117-24.
Syrjanen S. Human papillomavirus in head and neck cancer. *Journal of Clinical Virology* 2005; 32S; S59-S66.
Syrjanen K. HPV infections in benign and malignant sinonasal lesions. *Journal of Clinical Pathology.* 2003; 56(3): 174-81.

The Cost of Treating HPV-related Diseases

Malignant Diseases

Cancer of the Cervix

The costs of treating HPV-related cervical disease arise out of routine cervical screening, the detection and management of cervical precancers, and the treatment of cervical cancers. Insigna et al. offered the following breakdown of total costs derived from an observational cohort study of over 100,000 female enrollees in a major US health care plan in 1998: [597]

Routine cervical screening	- 64%
Dealing with false-positive results	- 9%
Management of cervical precancers	- 17%
Treating invasive cervical cancers	- 10%

Their detailed results are found on the following two tables. As seen in the first table, the cost of a negative pap smear, where follow-up was not indicated, was $57, while the average follow-up cost for an abnormal result was $732.

Cost per Episode of Care with Routine Smear Diagnosis	
Diagnosis	*Cost)*
Negative	$57
Atypical squamous cells (ASC)	$299
Atypical glandular cells (AGC)	$1,509
Low-grade squamous intraepithelial lesion (LSIL)	$1,275
High-grade squamous intraepithelial lesion (HSIL)	$2,349
Any abnormal result	$732
Note: 2002 US dollars; a US$ is currently valued at CDN $1.19.	

Among the approximately 31,000 Pap smears performed in the study cohort, the vast majority were negative; among the 5% showing positive readings, about 3% represented ASC, 0.2% AGC, 0.7% LSIL and 0.1% HSIL. Confirmed CIN or full cancer is even less frequent. Upon follow-up, CIN or cancer was detected in 10% of cases with ASC, 21% of cases with AGC, 46% of cases with LSIL, and 87% of cases with HSIL, which amounts to less than 1% of the total women screened. The actual cases of cancer would be even a smaller percentage.

[597] Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus--related disease. *American Journal of Obstetrics & Gynecology.* 2004; 191(1): 114-20.

The cost per outcome in the follow-up after a positive test ranged from $79 for an incomplete follow-up to $376 for a false positive smear to $1,709 for any cervical intraepithelial neoplasia (CIN), as indicated the table below.

Cost per Outcome of Follow-up	
Outcome	*Cost*
Incomplete follow-up	$79
False positive smear	$376
Cervical intraepithelial neoplasia 1	$1,026
Cervical intraepithelial neoplasia 2	$1,300
Cervical intraepithelial neoplasia 3	$3,235
Any CIN	$1,709
Note: 2002 US dollar;, a US$ is currently valued at CDN$1.19.	

Kim and co-authors provide information comparing direct medical costs associated with conventional cytology, colposcopy, biopsy, treatment of CIN 2/3, and stages of cervical cancers in four European countries, as indicated on the following table.[598]

Comparison of Medical Costs in European Countries				
Direct Medical Costs	*United Kingdom*	*The Netherlands*	*France*	*Italy*
Conventional Cytology	$40	$49	$14	$29
Colposcopy	$136	$106	NA	$101
Colposcopy and Biopsy	$248	$170	NA	$185
CIN 2/3	$678	$2,168	$908	NA
Local Invasive Cervical Cancer	$18,618	$6,642	$3,726	NA
Regional Invasive Cervical Cancer	$30,564	$13,740	$14,451	NA
Distant Invasive Cervical Cancer	$32,423	$21,466	$34,122	NA
Note: In 2004 US$, a US$ is currently valued at CDN$1.19.				

[598] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. *Journal of the National Cancer Institute.* 2005; 97(12): 888-95.

Kleinberg and colleagues examined the costs of various management strategies for cervical intraepithelial neoplasia (grades 2 and 3) in more detail.[599] Their estimated costs, as identified in the following table, are based on an average of the typical US Medicare reimbursement and that of a third-party payer in Alabama.

Cost of Management Strategies per Patient	
Procedure	*Cost*
Pap smear	$77
Colposcopy with biopsy	$303
Cryotherapy	$112
Carbon dioxide laser ablation	$3,267
Loop electrosurgergical excision procedure	$407
Cold-knife conization	$3,739
Total vaginal hysterectomy	$11,898
Laser ablation of vagina	$3,119
Partial vaginectomy	$5,338
Note: 2001 US dollars, a US$ is currently valued at CDN $1.19.	

Ano-Genital Cancers

Goldie et al. estimated the workup costs of low-grade anal squamous intraepithelial lesions at $147 (1997 US dollars).[600] This cost includes a high-resolution anoscopy and biopsy but no treatment. The workup and treatment costs of high-grade anal squamous intraepithelial lesions was estimated at $2,483; this included referral to a surgeon, one preoperative office visit with anoscopy, electrocautery or excisional biopsy using a colposcope and anesthesia in an outpatient surgical setting, postoperative oral analgesia for two weeks, and 1 postoperative visit at 30 days. The cost of treating and managing invasive anal cancer was estimated at $21,200.

The cost of a radical vulvectomy in the Netherlands has been estimated at €14,008 (2002 euros), which includes surgery costs (€2,277), hospital costs (€9,660), medications (€704), wound care materials (€186), diagnostic procedures / laboratory

[599] Kleinberg MJ, Straughn JM, Jr., Stringer JS et al. A cost-effectiveness analysis of management strategies for cervical intraepithelial neoplasia grades 2 and 3. *American Journal of Obstetrics & Gynecology.* 2003; 188(5): 1186-8.

[600] Goldie SJ, Kuntz KM, Weinstein MC et al. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *American Journal of Medicine.* 2000; 108(8): 634-41.

tests (€765), outpatient visits (€45), GP visits (€31), and care by a district nurse (€342).[601]

Cancers of the Head and Neck

Average treatment costs per new patient with a head and neck cancer in the Netherlands have been estimated at €31,829 (1996 prices). This includes the costs of treating the primary tumor, treating recurrent tumors, and 10 years of follow-up.[602] The study was based on 854 cancers, of which 40.0% were cancers of the oral cavity, 43.2% cancers of the larynx, and 16.8% cancers of the oropharynx. The costs for each of these head and neck cancers are summarized on the following table.

Average Costs per New Head and Neck Cancer Patient in the Netherlands				
	Oral Cavity	*Larynx*	*Oropharynx*	***Weighted Average***
Primary Tumor	€25,096	€16,860	€25,353	**€21,581**
Recurrent Tumor	€10,022	€9,568	€9,866	**€9,825**
Long-term Follow-up (10 Years)	€423	€423	€423	**€423**
Total per Patient	**€35,541**	**€26,851**	**€35,642**	**€31,829**
Note: 1996 prices, a € is currently valued at CDN $1.45.				

By comparison, the average US Medicare costs for elderly patients with squamous cell cancer of the head and neck were found to be $25,542 (1998 US dollars) higher than for matched controls.[603]

[601] Uyl-De Groot CA, Hartog JG, Derksen JG et al. Cost-effectiveness and quality of life of granulocyte-colony stimulating factor (filgrastim) after radical vulvectomy and bilateral inguino-femoral lymphadenectomy: results of a randomized clinical trial. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2004; 114(1): 77-82.

[602] van Agthoven M, van Ineveld BM, de Boer MF et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. *European Journal of Cancer.* 2001; 37(17): 2204-11.

[603] Lang K, Menzin J, Earle CC et al. The economic cost of squamous cell cancer of the head and neck: findings from linked SEER-Medicare data. *Archives of Otolaryngology Head & Neck Surgery.* 2004; 130(11): 1269-75.

In the Netherlands, a study estimating the cost of several different approaches to treating cancer of the tonsils found the price to be in the €14,262 to €18,782 range.[604] These costs included the work-up, treatment, potential relapse, and five years of follow-up, as indicated on the following table.

Treatment Modalities for Cancer of the Tonsils Mean Cost per Patient			
Cost Category	External Beam Radiotherapy and Brachytherapy	External Beam Radiotherapy and Brachytherapy and Neck Dissection	Surgery
Work-up	€1,761	€1,761	€1,761
Treatment	€6,377	€9,688	€13,178
Relapse	€5,498	€4,569	€3,318
5-Yr Follow-up	€626	€610	€604
Total	**€14,262**	**€16,628**	**€18,782**
Note: 2001 prices; a € is currently valued at CDN$1.45.			

In Greece, the hospitalization costs of treating oral cancers have been estimated to range from €3,815 to €11,950, depending on the stage of the cancer (see following table).[605]

Comparison of Hospital Costs for Oral Cancer In Greece		
Stage	*Average Length of Stay (in Days)*	*Cost*
I	14.6	€3,815
II	30.3	€6,112
III	34.3	€10,780
IV	39.0	€11,950
Note: 2001 prices; a € is currently valued at CND$1.45.		

[604] Nijdam W, Levendag P, Noever I et al. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(2): 488-94.

[605] Zavras A, Andreopoulos N, Katsikeris N et al. Oral cancer treatment costs in Greece and the effect of advanced disease. *BMC Public Health.* 2002; 2(1): 12.

Non-malignant Diseases

Genital Warts

A variety of treatment options are available to patients with genital warts. Kodner and colleagues have identified the following therapies used in the United States, together with the associated costs for treating both simple and extensive warts.[606]

Comparison of Treatment Costs for Genital Warts Cost per Successful Treatment		
Treatment	*Simple Warts*	*Extensive Warts*
Cryotherapy	$268	$415
Imiquimod	$607	$649
Interferon	$2,744	$5,803
Laser Treatment	$197	$535
Podofilox	$200	$334
Podophyllin Resin	$385	$1,449
Surgical Excision	$210	$318
Trichloroacetic Acid	$513	$966
Note: 2002 US dollars, a US$ is currently valued at CDN$1.19.		

On average, a complete episode of care in the United States costs $436 (2002 US$) and involve 3.1 physician visits.[607]

In England, the estimated cost per successful treatment is £222 ($404 in current US dollars) for males and £211($384 in current US dollars) for females, with an average number of clinic visits of 5.71 for males and 6.25 for females.[608,609]

In the Netherlands, a completed episode of care involved an average of 5.78 clinic visits for men and 6.52 clinic visits for women, at an average cost of €396 ($487 in current US dollars) and €485 ($597 in current US dollars) respectively.[610]

[606] Kodner CM, Nasraty S. Management of genital warts. *American Family Physician.* 2004; 70(12): 2335-42.
[607] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clinical Infectious Diseases.* 2003; 36(11): 1397-403.
[608] Langley PC, White DJ, Drake SM. Patterns of treatment and resource utilization in the treatment of external genital warts in England and Wales. *International Journal of STD and AIDS.* 2004; 15(7): 473-8.
[609] Langley PC, White DJ, Drake SM. The costs of treating external genital warts in England and Wales: a treatment pattern analysis. *International Journal of STD and AIDS.* 2004; 15(8): 501-8.
[610] van der Meijden WI, Notowicz A, Blog FB et al. A retrospective analysis of costs and patterns of treatment for external genital warts in The Netherlands. *Clinical Therapeutics.* 2002; 24(1): 183-96.

Recurrent Respiratory Papillomatosis

A study by Bishai and colleagues on the cost of juvenile-onset recurrent respiratory papillomatosis (RRP) used the following assumptions:[611]

- Duration of the disease – 4.2 years
- Number of surgeries per year – 4.4
- Each surgery is associated with 3 outpatient visits
- Cost of each surgery is $4,817 (in 1997 US$), including hospital, physician and outpatient costs
- Rate of tracheotomy – 14% of children over the 4.2 year period
- Cost of a tracheotomy estimated at $75,000 (in 1997 US$)

Using these assumptions, we have calculated an average cost per new case of juvenile-onset RRP as $99,500 (in 1997 US$).

RRP can take a variable course. The juvenile recurrent form tends to be aggressive and sometimes requires equally aggressive treatment. Most adults have a less aggressive form of the disease. Although there is a subset of adult-onset RRP that behaves similarly to the juvenile form, most adult cases are treated with fewer procedures than used with children.[612] One small study estimated that adults required 70% of the number of procedures required by juveniles.[613]

[611] Bishai D, Kashima H, Shah K. The cost of juvenile-onset recurrent respiratory papillomatosis. *Archives of Otolaryngology -- Head and Neck Surgery.* 2000; 126(8): 935-9.
[612] McClay JE. Recurrent Respiratory Papillomatosis (August 18, 2004) Available at http://www.emedicine.com/ent/topic594.htm. Accessed September, 2005.
[613] Long Y, Sani A. Recurrent respiratory papillomatosis. *Asian Journal of Surgery.* 2003; 26(2): 112-116.

Summary

A considerable amount of financial information is available in the literature with respect to treating HPV-related cervical disease, including the costs of routine cervical screening, the detection and management of cervical precancers, and the treatment of cervical cancers. Much less information is available, however, for the other malignant, as well as the non-malignant, diseases associated with HPV.

We have used the available costing information to generate the following results, with details on the assumptions made in generating these costs included in Appendix B.

Estimated Cost of Treating
HPV related Diseases in BC in 2005

	Cost / Case Procedure
Cervical Cancer	
Conventional Cytology	$ 40
Colposcopy	$ 139
Precancers	$ 984
Local Invasive Cervical Cancer	$ 11,716
Regional Invasive Cervical Cancer	$ 23,749
Distant Invasive Cervical Cancer	$ 35,979
Anogenital Cancers	
Vulva	$ 31,139
Vagina	$ 37,787
Penis	$ 37,787
Anus	$ 44,434
Cancers of the Head and Neck	
Tonsils	$ 26,103
Larynx	$ 47,912
Sinonasal	$ 63,599
Oral	$ 63,418
Non-Malignant Diseases	
Genital Warts	$ 549
Recurrent Respiratory Papillomatosis	
Children	$ 143,827
Adults	$ 100,679

Whenever possible, we have used costs from multiple sources and countries. We have also used data which take into account a fuller costing than just the direct one-time treatment costs of the cancers. For example, cancer treatment costs include assessment, treatment, recurrence and longer term follow-up costs.

Furthermore, the costs for RRP in children, for example, take into account the fact that the average child with RRP will require an average of 4 operations per year over an average 4.2 year time period.

HPV Vaccines

Vaccination can either be prophylactic (preventing contact with a virus from developing into an active infection) or therapeutic (clearing an existing infection). There has been a great deal of excitement and energy around creating and testing a vaccine targeting HPV. This has been a special focus in the context of developing countries, for two reasons: the bulk of the annual 200,000 deaths related to cervical cancer occur there (making it the most prevalent cause of female cancer mortality), and less than 5% of these women currently participate in the other major public health strategy, namely, screening.[614] As the potential launch date for an HPV vaccine nears, however, there are also questions regarding the applicability of such a vaccine in nations with comprehensive cervical screening programs. Indeed, this is the key question which prompted this background paper.

Many challenges exist in the development of a vaccine. Because of the multiplicity of HPV types which are oncogenic, there is motivation to make any vaccine polyvalent. This adds development and manufacturing expense, however, so the "balancing act" in terms of resource investment involves targeting those viral types which cause the greatest proportion of cancer. Once a strategy has been established, there still must be vigilance against the "potential epidemiological shift of HPV disease to currently less frequent types and variants."[615]

There have been several studies exploring either preventive or therapeutic HPV vaccines in humans.

Monovalent – HPV 16

The trial by Koutsky et al. reported in 2002 has provided the most conclusive evidence to date that HPV vaccination is both safe and effective.[616] The main objective of this double-blind, placebo-controlled, randomized trial was to determine whether an HPV 16 vaccine would prevent HPV 16 infection in women.

The study involved 2,392 women 16-23 years of age from 16 centres in the US who reported no prior abnormal Pap smear. The women were given three intramuscular injections of either a vaccine or placebo at 0, 2 and 6 months. Follow-up visits were scheduled one month after the third vaccination (Month 7), six months after the third vaccination (Month 12), and every six months thereafter until month 48 or the completion of the trial (with a median follow-up of 17.4 months after completion of the vaccination regimen). During these visits, specimens were collected for Pap tests, HPV 16 DNA testing, and measurement of HPV 16 antibodies.

Efficacy

The incidence of persistent HPV 16 infection (defined as having DNA detected on two or more consecutive visits four or more months apart) was 3.8 per 100 woman-years in the placebo group and 0 per 100 woman-years in the vaccine group, a 100%

[614] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer*. 2003; 106(6): 896-904.
[615] Padilla-Paz LA. Human papillomavirus vaccine: history, immunology, current status, and future prospects. *Clinical Obstetrics & Gynecology*. 2005; 48(1): 226-40.
[616] Koutsky LA, Ault KA, Wheeler CM et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine.* 2002; 347(21): 1645-51.

efficacy rate. All 41 cases of HPV 16 infection detected in the study occurred in the placebo group.

Thus, the vaccine not only prevented the development of disease, but also seems to prevent "its causative agent from residing in the genital tract where it can infect new sexual partners."[617] The main caveat emerging from this study was evidence that vaccination against one type of HPV will not protect against infection by different types. Another limitation is that the vaccine does not appear to reverse infection or cervical neoplasia once it is present.

Safety

The encouraging efficacy results were matched by an impressive safety profile. There were almost identical rate of adverse events when comparing the vaccine and placebo groups (see following table).

HPV Vaccines
Clinical Adverse Events

	HPV-16 Vaccine		Placebo	
	N	%	N	%
N=	1,130		1,150	
No adverse events	78	6.9%	96	8.3%
>=1 Adverse events	1,052	93.1%	1,054	91.7%
Pain at injection site	975	86.3%	947	82.3%
Systemic event	807	71.4%	824	71.7%
Vaccine-related adverse event	1,011	89.5%	1,007	87.6%
Pain at injection site	975	86.3%	947	82.3%
Systemic event	470	41.6%	500	43.5%
Serious adverse event	4	0.4%	3	0.3%
Serious vaccine-related adverse event	-	0.0%	-	0.0%
Discontinued study due to adverse event	4	0.4%	5	0.4%
Discontinued study due to vaccine-related adverse event	3	0.3%	4	0.3%
Discontinued study due to vaccine-related adverse event	-	0.0%	-	0.0%

*Source: Koutsky et al **NEJM** 2002*

The most common adverse event reported for both the vaccine and placebo groups was pain at the injection site. Although the vaccine was generally well tolerated and there were no serious vaccine-related adverse events, "a slightly higher percentage of women in the vaccine group than in the placebo group did not complete the vaccination series or withdrew shortly thereafter, suggesting that the vaccine may have been associated with reduced tolerability."[618]

[617] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[618] Koutsky LA, Ault KA, Wheeler CM et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine.* 2002; 347(21): 1645-51.

Bivalent – HPV 16/18

The results of the only other phase III trial were reported in November, 2004. The researchers studied the effect of a bivalent vaccine protecting against HPV 16 and HPV 18; adding HPV 18 creates the potential for eliminating another 10% of total cervical cancer cases.[619] The main objective of this double-blind, multi-centre, placebo-controlled, randomized trial was to assess the efficacy of a bivalent vaccine against incident and persistent infections with HPV 16 and HPV 18.

The study involved 1,113 women 15-25 years of age from 32 centres in the US, Canada and Brazil who were negative for a series of 14 high risk HPV types. The study took place in two phases: an initial phase for vaccination and follow-up that concluded at 18 months and a follow-up phase that ended at month 27. The women were given three doses of either a vaccine or placebo at 0, 1 and 6 months. Specimens were collected by health care providers for cytology and HPV DNA testing at months 6, 12 and 18. In addition, women self-collected cervicovaginal samples every three months.

Efficacy

In women who followed the full vaccination protocol, vaccine efficacy was 91.6% against incident infection and virtually 100% against persistent infection with HPV 16/18. Even when women did not adhere to the full vaccination protocol, vaccine efficacy was 95.1% against persistent infection with HPV 16/18, suggesting that the vaccine was highly efficacious even among the partially adherent subset. One woman in the vaccine group developed a persistent HPV 51 infection.

Safety

No serious adverse events occurred in either the vaccine or placebo groups. The event rates were basically similar in the two groups, though the vaccine group had more injection site symptoms, as indicated on the following table.

[619] Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *The Lancet.* 2004; 364(9447): 1757-65.

HPV Vaccines
Clinical Adverse Events

	HPV-16/18 Vaccine		Placebo		p Value
	N	%	N	%	
N=	531		538		
Seriuos adverse events					
Related to vaccination	-	0.0%	-	0.0%	
During study	22	4.1%	19	3.5%	0.636
Injection site symptoms					
Pain	496	93.4%	469	87.2%	0.0006
Swelling	182	34.3%	113	21.0%	<0.0001
Redness	189	35.6%	131	24.3%	0.0001
Overall	499	94.0%	472	87.7%	0.0004
General Symptoms					
Fatigue	308	58.0%	289	53.7%	0.175
Gastrointestinal	178	33.5%	172	32.0%	0.602
Headache	331	62.3%	329	61.2%	0.706
Itching	130	24.5%	109	20.3%	0.106
Rash	60	11.3%	54	10.0%	0.552
Raised temperature	88	16.6%	73	13.6%	0.172
Overall	458	86.3%	462	85.9%	0.860
Withdrawal from study					
Due to non-serious adverse event	-	0.0%	3	0.6%	0.249
Due to serious adverse event	1	0.2%	-	0.0%	0.497

*Source: Harper et al **Lancet** 2004*

The authors note, however, that even the injection site symptoms tended to be mild and transient and had no effect on adherence to the vaccination course.

One woman in the vaccine group dropped out of the study because of a serious adverse event (spontaneous abortion) that was not related to vaccination.

Quadrivalent – HPV 16/18/6/11

Several other studies have reported on earlier phases of vaccine testing. The phase II data from a quadrivalent vaccine published in May, 2005, are very promising.[620] This study examined the effect of a quadrivalent vaccine protecting against HPV 16 and HPV 18, as well as HPV 6 and 11; adding the latter two types has the potential for protecting against non-malignant diseases such as genital warts and recurrent respiratory papillomatosis. The main objective of this double-blind, placebo-controlled, randomized trial was to assess the efficacy of a quadrivalent vaccine targeting the HPV types associated with 70% of cervical cancers and 90% of genital warts.

The study involved 1,158 women 16-23 years of age from Brazil, Europe and the US who had no seriously abnormal Pap smears. The study, however, did not exclude women with previous HPV infection. The study took place in two phases: an initial phase studying vaccine safety and a further phase assessing immunogenicity and efficacy. The women were given three doses of either a vaccine (at one of three

[620] Villa LL, Costa RL, Petta CA et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncology.* 2005; 6(5): 271-8.

different dose levels) or placebo at day 1, month 2 and month 6. Gynaecological examinations were done at day 1 and months 7, 12, 24 and 36; specimens were collected at these times as well as at months 18 and 30.

Efficacy

Over the 30 month follow-up, the vaccine reduced the combined incidence of persistent infection from HPV 16/18/6/11—as well as related genital disease such as cervical pre-cancers and genital warts—by 90%. The incidence of persistent infection did not differ between the high-dose, intermediate-dose or low-dose vaccination, leading the investigators to use the low-dose approach in the phase III clinical trials currently under way.

Safety

There were no serious vaccine-related adverse events. As indicated on the following table, injection site adverse events were higher in women receiving the vaccine than in those receiving the placebo, confirming the findings of previous studies. The vast majority of these adverse events involved pain of mild or moderate intensity.

HPV Vaccines
Clinical Adverse Events

	HPV - 6/11/16/18 Vaccine		Placebo	
	N	%	N	%
N=	272		274	
Adverse events reported	250	91.9%	242	88.3%
Injection site	234	86.0%	212	77.4%
Systemic	187	68.8%	190	69.3%
Vaccine-related adverse event	243	89.3%	225	82.1%
Injection site	234	86.0%	212	77.4%
Systemic	104	38.2%	90	32.8%
Serious adverse event	2	0.7%	2	0.7%

*Source: Villa et al **Lancet Onc**. 2005*

Conclusion

Based on these three studies, it appears that a vaccine for HPV is both highly efficacious and very well-tolerated. Efficacy ranges from 90 to 100%. The lower efficacy seems to be seen when vaccination protocols are not completely followed or when vaccines target multiple HPV types in a less select group of women (e.g., including those with a previous HPV infection).

As one or more of these vaccine products move towards licensing in the next few years, several questions remain open:

- Who should be vaccinated, and when? Some argue that the key population should be girls before they are sexually active; but since HPV causes a variety of cancers in men and women, a case can also be made to vaccinate everyone.[621,622]
- How long does the protection last? Follow-up periods of up to three years indicate that between 89 and 94% of women were still seropositive, i.e., they had antibody titres to HPV 6, 11, 16 and 18.[623] Longer studies will be required to determine whether and when booster doses will be required.
- How polyvalent should a widely-used public health vaccine be? For example, if women were vaccinated against five HPV types (16, 18, 31, 33, and 45), it would reduce cervical cancer risk by 85%.[624] Another consideration is mortality; one study showed that cervical cancer patients with HPV 18 or 45 are more likely to die from their disease.[625]
- How effective and cost-effective would a vaccination program be over the long-term, especially compared to current screening strategies? We turn to this question in the next sections of this report.

[621] Winer RL, Koutsky LA. Human papillomavirus through the ages. *Journal of Infectious Diseases.* 2005; 191(11): 1787-9.
[622] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[623] Villa LL, Costa RL, Petta CA et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncology.* 2005; 6(5): 271-8.
[624] Crum CP. The beginning of the end for cervical cancer? *New England Journal of Medicine.* 2002; 347(21): 1703-5.
[625] Wright JD, Li J, Gerhard DS et al. Human papillomavirus type and tobacco use as predictors of survival in early stage cervical carcinoma. *Gynecologic Oncology.* 2005; in press: 8 pp.

Modelling the Implementation of an HPV Vaccination Program

We raised the vital issue of the cost-effectiveness of any vaccination program at the end of the previous section. How would a program perform over the long-term, especially compared to current screening strategies? Researchers have attempted to address this question through mathematical modeling of disease progression and the impact of a vaccine.[626,627] We will review the results of some of these efforts below.

The Impact of an HPV Vaccination Program

Hughes et al. developed a model to assess the most effective strategy for vaccination and the likely impact of a vaccine on both HPV and cancer incidence. [628] More specifically, they addressed the following questions:

1. Should vaccines be focussed on high risk population groups or administered more widely?

2. Should both men and women be vaccinated, or can a program targeted at only women be effective?

Under a specific set of assumptions (90% vaccine coverage, 75% vaccine effectiveness, mean 10-year immunity) they found that vaccinating both men and women leads to a 44% decrease in the endemic prevalence of whichever HPV types are targeted. In contrast, vaccinating only women leads to a 30% decrease in HPV prevalence. Over a broad range of assumptions, female-only vaccination is likely to be between 60% and 75% as efficient as a strategy that targets both sexes. At the same time, targeting the vaccine only at high-risk groups is unlikely to succeed because these groups would be difficult to identify and cover.

A further finding of their model is that a 60% reduction in the incidence of high-risk HPV would only lead to a 47% reduction in cervical cancers. This is due to a 'replacement effect' in which some of the cancers avoided through vaccination would be replaced by HPV–related cancers not covered by the vaccine. Since vaccines are unlikely to completely eliminate a woman's risk of cervical cancer, the authors suggest that screening programs would need to continue in some form.

Sanders and Taira modelled the effectiveness and cost-effectiveness of a prophylactic HPV vaccine provided to all 12-year-old girls in the US.[629] They assumed that the vaccine would be 75% effective against high-risk HPV types (i.e., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), that 70% of 12-year-old girls would comply with the vaccination program, and that a booster shot would be required after 10 years. Based on these and other assumptions detailed in their study, they estimated that vaccinating the current cohort of 1,988,600 12-year-old girls in the US would result in 224,255 cases of HPV infection averted, 112,710 cases of SIL averted, 3,317

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[626] Cantor SB, Fahs MC, Mandelblatt JS et al. Decision science and cervical cancer. *Cancer.* 2003; 98(9 Suppl): 2003-8.
[627] Goldie SJ. Health economics and cervical cancer prevention: a global perspective. *Virus Research.* 2002; 89(2): 301-9.
[628] Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology.* 2002; 13(6): 631-9.
[629] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases.* 2003; 9(1): 37-48.

cases of cervical cancer averted, and 1,340 cervical-cancer deaths averted over the cohort's lifetime. Overall, such a program would increase the life-expectancy of this cohort by 2.8 days (4.0 quality adjusted days) at an incremental cost of $246 per person. This translates into an incremental cost effectiveness of the HPV vaccination program of $22,755 per QALY.

In the discussion of their results, Sanders and Taira note that vaccination programs against measles, mumps, rubella, and pertussis save 2.7, 3.0, 0.3, and 3.3 life days, respectively. Furthermore, "although HPV is most commonly associated with cervical cancer, it may also play a role in cancers of the anus, vulva, vagina, and penis…. Including (these cancers) should make HPV vaccination even more favourable."

In a follow-up study, Taira and colleagues estimated that a vaccine targeting HPV 16 and 18 provided to 12-year-old girls would reduce cervical cancer cases by 61.8%, with a cost-effectiveness of $14,583 per QALY.[630] Including males in the vaccine rollout would increase the reduction in cervical cancer cases by only about 2% (i.e., to 63.9%) at an incremental cost-effectiveness of $442,039 per QALY. The authors conclude that "including male participants in a vaccination program is generally not cost-effective, compared to female-only vaccination".

Goldie et al. modelled the impact of a HPV 16/18 vaccine using the following basic assumptions: [631]

- An effective vaccine would reduce the probability of acquiring persistent infection with HPV 16/18 by 50%, 75% or 98%.
- 100% of the cohort (13-year-old adolescent girls) is successfully vaccinated prior to their first exposure to HPV.
- Adolescents receive 3 doses of the vaccine and are fully immunized by age 13, when the simulation begins.
- Recipients of an effective vaccine are subject to the competing risks associated with acquisition of other HPV types.
- Vaccination has no impact on HPV 16/18 infections that are destined to be transient.
- Vaccine efficacy does not wane over time.

An HPV 16/18 vaccine with 98% effectiveness was associated with a 51% reduction in overall cervical cancers, while 75% effectiveness resulted in a 44% reduction.

Two critical assumptions are the estimated proportion of the population who are successfully vaccinated and the potential waning immunity over time. If, for example, only 75% of the base population is vaccinated (rather than the 100% assumed in the base case scenario), then the reduction in overall cancers would decrease from 51% (in 98% efficacy scenario) to approximately 38%. If the decrease in projected vaccine benefit attributable to waning over a 10-year period was 25%,

[630] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerging Infectious Diseases.* 2004; 10(11): 1915-23.
[631] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer*. 2003; 106(6): 896-904.

then the overall decrease in efficacy would be from 2-10% (with this range dependent on another assumption, namely, the degree to which cervical cancers later in life are due to 'new' HPV infections or due to the reactivation of latent infections acquired during the years when the vaccine is maximally effective). If the decrease in projected vaccine benefit attributable to waning over a 10-year period was 100%, then the overall decrease in efficacy would be from 10-57%.

Combining HPV Vaccination and Screening Programs

In a subsequent analysis, Goldie and co-authors addressed a broader question, namely, the introduction of an HPV 16/18 vaccine in a population with an organized screening program.[632] They estimated the cost-effectiveness of implementing an HPV 16/18 vaccine in the context of current screening practices in the US. The cost per QALY ranged from $20,600 (2002 US dollars) per QALY if the vaccine is 100% effective in preventing persistent HPV 16/18 infections to $33,700 if the vaccine is only 70% effective. They then addressed the potential effect of a screening program (either conventional or liquid-based cytology) with or without a vaccination program. Further variables included the age of screening onset (ranging from age 18 to 35) and the frequency of screening (ranging from every 1 to 5 years).

A program which included a conventional screening every three years starting at age 25, together with a vaccination program, resulted in a 94% reduction in the life-time risk of cervical cancer[633] at a cost of $58,500 per QALY. A conventional screening program alone resulted in a reduction in the life-time risk of cervical cancer of 67% to 74% (test conducted every five years, with the range of impact depending on the age of initiation). At the extreme end of the analysis was an annual liquid-based screening program starting at age 18, together with a vaccination program. While this approach resulted in a 99% reduction in the life-time risk of cervical cancer, the cost per QALY was almost $3.9 million.

Kulasingam and Myers also addressed the issue of adding an HPV 16/18 vaccine to current screening programs.[634] They examined the following three strategies:

1. One-time vaccination of 12-year-old girls only.
2. Conventional cytology-based screening only.
3. One-time vaccination of 12-year-old girls followed by a cytology-based screening program.

They also included a range for the age of screening onset (from age 18 to 30) and the frequency of screening (from every 1 to 5 years). Their analysis suggested that a vaccination program with screening every two years beginning at age 24 would result in a reduction in the incidence of cervical cancer of 82.6% and a reduction in mortality from cervical cancer of 89.8% (compared to no vaccine or screening

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[632] Goldie SJ, Kohli M, Grima D et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute.* 2004; 96(8): 604-15.

[633] A number of studies have estimated a lifetime cervical cancer risk of 3.67% and a lifetime cervical cancer mortality risk of 1.26%. See Myers ER, McCrory DC, Nanda K et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *American Journal of Epidemiology.* 2000; 151(12): 1158-71. Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer.* 2003; 106(6): 896-904.

[634] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *Journal of the American Medical Association.* 2003; 290(6): 781-9.

programs). The cost of the program would be $44,889 (2001 US dollars) per life-year saved. A vaccination program together with annual screening beginning at age 18 would reduce the incidence of and mortality from cervical cancer by 93.2% and 96.6%, respectively, but at a cost of $236,250 per life-year gained.

Summary

The mathematical modeling of disease progression and the impact of a vaccine is complex, requiring a host of assumptions reflecting incomplete knowledge. As noted by one author, "the very nature of models requires that they make unrealistic assumptions."[635] Despite these limitations, cost-effectiveness analysis and disease-simulation models provide valuable information in the absence of real-world experience. Capitalizing on data from multiple sources, models "can serve as a valuable tool to extend the time horizon of clinical trials, to evaluate more strategies than possible in a single clinical trial, and to assess the relative costs and benefits of alternative policies to reduce mortality from cervical cancer."[636]

Whatever their utility, vaccination modeling must be handled with caution. In addition to incomplete knowledge regarding potential vaccines (e.g., effectiveness, uptake in the population, waning, etc.), there are a number of other important limitations when designing models. First, our understanding of the relationship between cancers and HPV is still evolving (as noted earlier in this report). Second, it is difficult to simulate sexual contact patterns among groups of people. Third, infectious agents are rarely static, with various HPV strains likely to have differing transmission dynamics. Fourth, it is difficult to model the natural history of multiple HPV infections. Fifth, it is important to assess if there is any cross-protection against other strains of the virus when vaccinated for one type of HPV. Sixth, there is the question of whether persistent HPV infections in older women represent a reactivation of latent or previously acquired HPV, or a brand new infection.

A key issue is the preference of patients and their parents. A number of the models have assumed a 100% uptake of the vaccine in 12-year-old girls. Will parents accept a vaccine targeted at a sexually transmitted disease, particularly one that is only partially effective given the variety of HPV types that can be contracted? A recent study by Davis et al. found that 55% of parents would accept an HPV vaccine for their 10 to 15-year-old children, 22% would not and 23% were undecided.[637] After a brief written educational intervention, 74% would accept the vaccine, 18% would not and 8% remained undecided. Interestingly, they found that concerns about potential side effects, religious values, and knowledge of HPV were not barriers to vaccine acceptance. Education and ethnicity also were not predictors of who would take up the vaccine. As noted in a recent review, "acceptance could be increased by emphasizing the anticancer aspects of the vaccine, but it would be difficult and deceptive to ignore the connection to sexual transmission."[638]

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[635] Koopman JS. Modeling infection transmission- the pursuit of complexities that matter. *Epidemiology.* 2002; 13(6): 622-4.
[636] Goldie SJ. Chapter 15: Public health policy and cost-effectiveness analysis. *Journal of the National Institute Monographs.* 2003; (31): 102-10.
[637] Davis K, Dickman ED, Ferris D et al. Human papillomavirus vaccine acceptability among parents of 10- to 15-year-old adolescents. *Journal of Lower Genital Tract Disease.* 2004; 8(3): 188-94.
[638] Schiller JT, Davies P. Delivering on the promise: HPV vaccines and cervical cancer. *Nature Reviews Microbiology.* 2004; 2(4): 343-7.

While the modelling research completed to date has a number of significant limitations, there are several consistent themes that appear. First, an HPV vaccination program would have a similar impact as that of a number of other routinely accepted vaccination programs. Second, a vaccination program targeting 12-year-old girls appears to be the most cost-effective approach. Including boys in a vaccination program improves the effectiveness of such a program, but only modestly at a high cost. Third, an HPV vaccination program will not eliminate the need for screening programs but may allow for later initiation and less frequent testing. And fourth, implementing a combined vaccination and screening program that would reduce the life-time mortality from cervical cancer by approximately 90% would cost in the neighbourhood of $45,000 to $60,000 (2002 US dollars) per QALY gained.

The Clinical Burden of HPV Infection in British Columbia

Malignant Diseases

In determining the clinical burden of HPV infection in British Columbia, we began with current B.C. Cancer Agency data on both the actual number of new cervical cancer cases in the province and projections to the year 2018. For the relevant anogenital cancers (vagina, vulva, anus, penis) and the relevant head and neck cancers (larynx, oral cavity, nasal cavity, tonsil, conjunctiva), we accessed information on the number of new cases over the five-year period from January 1, 1999 to December 31, 2003. The average five-year rate was then applied to B.C. population projections to estimate the annual number of new cases in the province to the year 2018 (see Appendix A for details). The results are indicated on the following table.

Projected New Cancer Cases in Britsh Columbia
HPV Related Cancers

	Cervix		Anogenital		Head & Neck		TOTAL		
	M	F	M	F	M	F	M	F	Total
2003		151	37	122	132	41	**169**	**314**	***483***
2004		150	38	125	136	42	**174**	**316**	***490***
2005		147	39	127	139	43	**178**	**317**	***495***
2006		145	39	130	143	44	**182**	**318**	***500***
2007		142	41	132	147	45	**187**	**319**	***506***
2008		140	42	135	150	46	**192**	**321**	***513***
2009		137	43	137	154	47	**197**	**321**	***518***
2010		135	44	140	158	48	**202**	**323**	***525***
2011		132	45	143	162	49	**207**	**324**	***531***
2012		130	46	145	166	51	**212**	**326**	***538***
2013		128	47	148	170	52	**217**	**327**	***545***
2014		126	48	150	174	53	**222**	**329**	***551***
2015		123	49	153	178	54	**227**	**330**	***557***
2016		120	50	155	183	55	**233**	**331**	***563***
2017		118	51	158	187	57	**238**	**333**	***570***
2018		115	52	161	191	58	**243**	**334**	***577***

In 2003, for example, we identified that there were 151 new cases of cervical cancer, 159 new cases of anogenital cancers with potential HPV infection, and 173 new cases of head and neck cancers with potential HPV infection.

While there is virtually a 100% correlation between cervical cancers and HPV infection, this is not the case for most of the other cancers, as indicated earlier in this report. Based on the best available data, HPV infection is directly involved in the following proportion of cancers:

Cancer	HPV Involvement
Cervix	100%
Anus	88%
Vulva	55%
Vagina	54%
Tonsil	51%
Conjunctiva	50%
Penis	42%
Larynx	25%
Oral	22%
Nasal	22%

These proportions were applied to the previous table and used to calculate the number of cervical, anogenital and head and neck cancers in B.C. attributable to HPV infection (see following table).

Projected New Cancer Cases in Britsh Columbia
Due to HPV Infection

	Cervix		Anogenital		Head & Neck		TOTAL		
	M	F	M	F	M	F	M	F	Total
2003		151	19	69	43	13	**61**	**233**	***294***
2004		150	19	71	44	13	**63**	**234**	***297***
2005		147	20	72	45	14	**64**	**233**	***297***
2006		145	20	73	46	14	**66**	**232**	***298***
2007		142	20	75	47	14	**68**	**231**	***299***
2008		140	21	76	48	14	**69**	**231**	***300***
2009		137	21	78	49	15	**71**	**230**	***301***
2010		135	22	79	51	15	**73**	**230**	***302***
2011		132	22	81	52	16	**74**	**228**	***303***
2012		130	23	82	53	16	**76**	**228**	***304***
2013		128	23	84	54	16	**78**	**228**	***306***
2014		126	24	85	55	17	**79**	**228**	***307***
2015		123	24	87	57	17	**81**	**227**	***308***
2016		120	25	88	58	17	**83**	**226**	***309***
2017		118	25	90	59	18	**85**	**226**	***310***
2018		115	26	91	60	18	**86**	**224**	***311***

Thus, while there were an estimated 483 new HPV-related cervical, anogenital and head and neck cancers in 2003 in B.C., only 294 (61%) of these cancers are directly associated with HPV infection.

HPV 16 and 18 are the most common types associated with cancers, but they are clearly not the only types so implicated. It is useful to calculate the proportion of the 294 new cancers in 2003, and so on for the other years, that would be associated with HPV 16/18 infection in particular. Based on the best available data, as noted earlier

in the report, HPV 16/18 infection is involved in the following proportion of each type of cancer:

Cancer	*HPV 16/18 Involvement*
Cervix	66%
Anus	80%
Vulva	100%
Vagina	71%
Tonsil	84%
Conjunctiva	100%
Penis	63%
Larynx	100%
Oral	100%
Nasal	100%

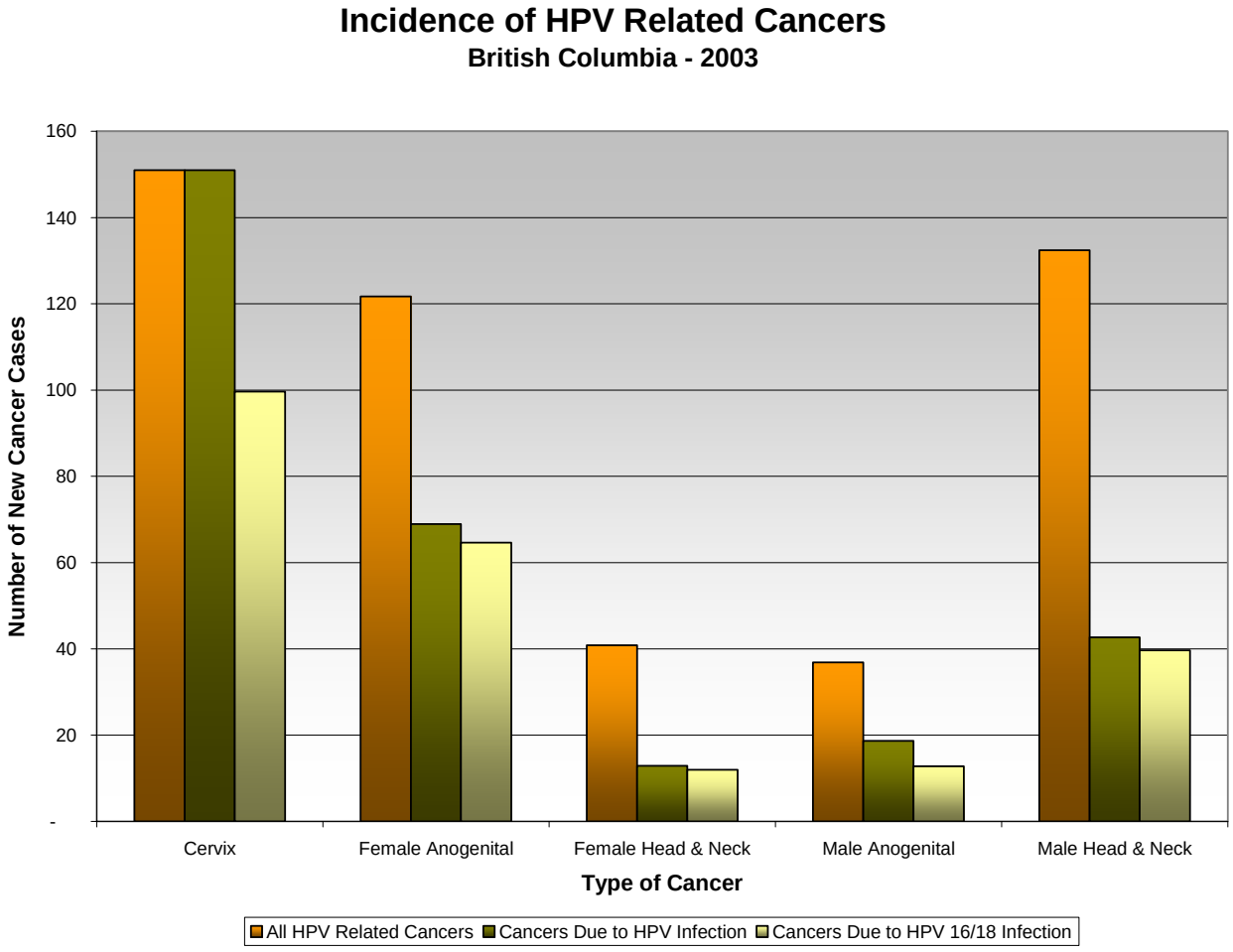
These proportions were used to calculate the number of cervical, anogenital and head and neck cancers in B.C. due to HPV 16/18 infection (see following table).

Projected New Cancer Cases in Britsh Columbia
Due to HPV 16/18 Infection

	Cervix		Anogenital		Head & Neck		TOTAL		
	M	F	M	F	M	F	M	F	Total
2003		100	13	65	40	12	**52**	**176**	***229***
2004		99	13	66	41	12	**54**	**177**	***231***
2005		97	13	67	42	13	**55**	**177**	***232***
2006		96	14	69	43	13	**56**	**177**	***234***
2007		94	14	70	44	13	**58**	**177**	***235***
2008		92	14	71	45	13	**59**	**177**	***237***
2009		90	15	73	46	14	**61**	**177**	***238***
2010		89	15	74	47	14	**62**	**177**	***240***
2011		87	15	76	48	14	**64**	**177**	***241***
2012		86	16	77	49	15	**65**	**178**	***243***
2013		84	16	78	51	15	**67**	**178**	***244***
2014		83	16	80	52	15	**68**	**178**	***246***
2015		81	17	81	53	16	**70**	**178**	***247***
2016		79	17	82	54	16	**71**	**178**	***249***
2017		78	17	84	55	17	**72**	**178**	***251***
2018		76	18	85	56	17	**74**	**178**	***252***

For example, of the 294 cancers directly associated with HPV infection in 2003, 229 (78%) are associated with HPV 16/18 in particular. The remainder of the new cases (a total of 65) are associated with a variety of other HPV types (e.g., 3 new cases are associated with HPV 6/11; see Appendix A).

Information on the number of new cancer cases in B.C. in 2003 that were potentially related to HPV infection, the subset actually attributable to HPV infection, and those associated with HPV 16/18 infection in particular is summarized on the following chart. The standard categories are displayed: cervical, male / female anogenital, and male / female head and neck.



Non-Malignant Diseases

To estimate the annual number of cases of genital warts, recurrent respiratory papillomatosis, and sinonasal papilloma, we applied incidence rates found in the literature (see *The Clinical Burden of HPV* section above) to the B.C. population. We were unable to find appropriate information on incidence rates for conjunctival papilloma.

Based on the best available information, we estimated that there were 6,985 new cases of genital warts, 6 cases of recurrent respiratory papillomatosis in children and 59 in adults, and 25 new cases of sinonasal papilloma in 2003 due to HPV infection (see following table). The data was projected until the year 2018.

Non-Malignant Disease HPV-Related Disease
Estimated Annual Incidence in British Columbia

	Genital Warts		RPP - Children		RPP - Adults		Sino-Nasal	
	M	F	M	F	M	F	M	F
2003	3,415	3,570	3	3	29	30	19	6
2004	3,445	3,608	3	3	29	30	19	6
2005	3,478	3,647	3	3	30	31	19	6
2006	3,517	3,685	3	3	30	31	19	6
2007	3,562	3,723	3	3	31	32	19	6
2008	3,610	3,756	3	3	31	32	20	7
2009	3,660	3,788	3	3	32	33	20	7
2010	3,711	3,823	3	3	32	33	20	7
2011	3,762	3,858	3	3	33	34	20	7
2012	3,809	3,889	3	3	33	34	21	7
2013	3,854	3,918	3	3	33	35	21	7
2014	3,899	3,944	3	3	34	35	21	7
2015	3,943	3,969	3	3	34	36	21	7
2016	3,983	3,992	3	3	35	36	22	7
2017	4,020	4,012	3	3	35	37	22	7
2018	4,050	4,028	3	3	36	37	22	7

The vast majority of these non-malignant diseases are associated with HPV types 6 and/or 11. In fact, an estimated 90% of genital warts, 76% of recurrent respiratory papillomatosis and 33% of sinonasal papilloma cases are caused by HPV 6/11. This information was combined with the information on the table above to calculate the incidence of non-malignant diseases due to HPV 6/11 infection in particular (see following table).

Non-Malignant Disease HPV-Related Disease
Due to HPV 6/11 Infection

	Genital Warts		RPP - Children		RPP - Adults		Sino-Nasal	
	M	F	M	F	M	F	M	F
2003	3,073	3,213	3	2	22	23	6	2
2004	3,100	3,248	2	2	22	23	6	2
2005	3,130	3,282	2	2	23	24	6	2
2006	3,165	3,317	2	2	23	24	6	2
2007	3,206	3,351	2	2	23	24	6	2
2008	3,249	3,380	2	2	24	25	7	2
2009	3,294	3,409	2	2	24	25	7	2
2010	3,340	3,441	2	2	24	25	7	2
2011	3,385	3,472	2	2	25	26	7	2
2012	3,428	3,500	2	2	25	26	7	2
2013	3,468	3,526	2	2	26	27	7	2
2014	3,509	3,550	2	2	26	27	7	2
2015	3,548	3,572	2	2	26	27	7	2
2016	3,585	3,593	2	2	27	28	7	2
2017	3,618	3,611	2	2	27	28	7	2
2018	3,645	3,625	2	2	27	28	7	2

For example, we estimated that there were 6,286 new cases of genital warts, 5 cases of recurrent respiratory papillomatosis in children and 45 in adults, and 8 new cases of sinonasal papilloma in 2003 due to HPV 6/11 infection. The figures for subsequent years have been projected. In particular, the data for 2005 will be used in the financial analysis which follows.

The Cost of Treating HPV-related Diseases in British Columbia

We combined the costing of HPV-related disease treatment found earlier in this report with the incidence data generated in the previous section, in order to estimate the total direct costs of HPV infections in B.C. for 2005. The results are provided on the following tables, first for all types of HPV, and then limited to types 16/18 and 6/11 (see Appendix B for details).

By All HPV Types

In 2005, we estimate the direct cost of HPV-related disease in B.C. to be $50.1 million annually (see following table).

Estimated Cost of HPV Infection in British Columbia
in 2005 By Gender

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	577,718	$ 40	$ 23,118,039		**$ 23,118,039**
False Positives			$ 3,250,000		**$ 3,250,000**
Cervical Precancers			$ 6,100,000		**$ 6,100,000**
Local Invasive Cervical Cancer	49	$ 11,716	$ 574,096		**$ 574,096**
Regional Invasive Cervical Cancer	49	$ 23,749	$ 1,163,699		**$ 1,163,699**
Distant Invasive Cervical Cancer	49	$ 35,979	$ 1,762,949		**$ 1,762,949**
Anogenital Cancers					
Vulva	54	$ 31,139	$ 1,681,528		**$ 1,681,528**
Vagina	12	$ 37,787	$ 453,443		**$ 453,443**
Penis	13	$ 37,787		$ 491,230	**$ 491,230**
Anus	12	$ 44,434	$ 266,607	$ 266,607	**$ 533,213**
Cancers of the Head and Neck					
Tonsils	26	$ 26,103	$ 156,099	$ 522,591	**$ 678,689**
Larynx	24	$ 47,912	$ 183,983	$ 965,908	**$ 1,149,891**
Sinonasal	5	$ 63,599	$ 190,796	$ 127,197	**$ 317,993**
Oral	2	$ 63,418	$ 63,418	$ 63,418	**$ 126,837**
Non-Malignant Diseases					
Genital Warts	6,286	$ 549	$ 1,724,154	$ 1,724,154	**$ 3,448,308**
Recurrent Respiratory Papillomatosis					
Children	5	$ 143,827	$ 359,566	$ 359,566	**$ 719,133**
Adults	45	$ 100,679	$ 2,265,268	$ 2,265,268	**$ 4,530,536**
Total			**$ 43,313,644**	**$ 6,785,940**	**$ 50,099,584**

Most of these costs are associated with the female population ($43.3 million or 86%), particularly in regard to the cervical screening program. Costs in the male population are estimated at $6.8 million.

By Specific HPV Types

The following tables show the specific costs in 2005 when the disease burden is limited to the four key HPV types which are the possible focus of a vaccination program.

The annual costs associated with HPV 16/18 infection amount to $28.6 million (or 57% of the $50.1 million total).

Estimated Cost of HPV Infection in British Columbia
in 2005 for HPV 16/18

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	381,294	$ 40	$ 15,257,905		**$ 15,257,905**
False Positives			$ 2,145,000		**$ 2,145,000**
Cervical Precancers			$ 4,026,000		**$ 4,026,000**
Local Invasive Cervical Cancer	32	$ 11,716	$ 378,903		**$ 378,903**
Regional Invasive Cervical Cancer	32	$ 23,749	$ 768,042		**$ 768,042**
Distant Invasive Cervical Cancer	32	$ 35,979	$ 1,163,546		**$ 1,163,546**
Anogenital Cancers					
Vulva	54	$ 31,139	$ 1,681,528		**$ 1,681,528**
Vagina	9	$ 37,787	$ 321,945		**$ 321,945**
Penis	8	$ 37,787		$ 309,966	**$ 309,966**
Anus	10	$ 44,434	$ 213,285	$ 213,285	**$ 426,571**
Cancers of the Head and Neck					
Tonsils	22	$ 26,103	$ 131,123	$ 438,976	**$ 570,099**
Larynx	24	$ 47,912	$ 183,983	$ 965,908	**$ 1,149,891**
Sinonasal	5	$ 63,599	$ 190,796	$ 127,197	**$ 317,993**
Oral	2	$ 63,418	$ 63,418	$ 63,418	**$ 126,837**
Non-Malignant Diseases					
Genital Warts	-	$ 549	$ -	$ -	**$ -**
Recurrent Respiratory Papillomatosis					
Children	-	$ 143,827	$ -	$ -	**$ -**
Adults	-	$ 100,679	$ -	$ -	**$ -**
Total			**$ 26,525,474**	**$ 2,118,752**	**$ 28,644,225**

The annual costs associated with HPV 6/11 infection amount to $8.8 million (or 18% of the $50.1 million total).

Estimated Cost of HPV Infection in British Columbia in 2005 for HPV 6/11

	Estimated New Cases in 2005	Cost / Case Procedure	Female	Male	Total
Cervical Cancer					
Conventional Cytology	-	$ 40	$ -		**$ -**
False Positives			$ -		**$ -**
Cervical Precancers			$ -		**$ -**
Local Invasive Cervical Cancer	-	$ 11,716	$ -		**$ -**
Regional Invasive Cervical Cancer	-	$ 23,749	$ -		**$ -**
Distant Invasive Cervical Cancer	-	$ 35,979	$ -		**$ -**
Anogenital Cancers					
Vulva	-	$ 31,139	$ -		**$ -**
Vagina	1	$ 37,787	$ 37,636		**$ 37,636**
Penis	1	$ 37,787		$ 40,772	**$ 40,772**
Anus	-	$ 44,434	$ -	$ -	**$ -**
Cancers of the Head and Neck					
Tonsils	1	$ 26,103	$ 4,683	$ 15,678	**$ 20,361**
Larynx	-	$ 47,912	$ -	$ -	**$ -**
Sinonasal	-	$ 63,599	$ -	$ -	**$ -**
Oral	-	$ 63,418	$ -	$ -	**$ -**
Non-Malignant Diseases					
Genital Warts	6,286	$ 549	$ 1,724,154	$ 1,724,154	**$ 3,448,308**
Recurrent Respiratory Papillomatosis					
Children	5	$ 143,827	$ 359,566	$ 359,566	**$ 719,133**
Adults	45	$ 100,679	$ 2,265,268	$ 2,265,268	**$ 4,530,536**
Total			**$ 4,391,307**	**$ 4,405,438**	**$ 8,796,746**

Adding the totals in the two tables, we find that the direct costs related to HPV 16/18/6/11 are about $37.4 million, or 75% of the total when all HPV types are considered. As described in the clinical information provided earlier in this report, the impact of HPV 6/11 is primarily seen in the non-malignant disease, with only a modest showing in a few cancers.

Modelling the Implementation of an HPV Vaccination Program in B.C.

Estimating the Cost of an HPV Vaccination Program

Having established the direct costs of HPV-related disease and prorated those costs according to the specific impact of four key viral types, the next step is to understand how much a vaccination program would cost. To develop this understanding, we considered different factors related to the initial vaccination and any booster phase.

1. Cost of vaccine materials, personnel and administration—range seen in the literature.
   - $300 (2001 US dollars), three-injection protocol[639,640]
   - $377 (2002 US dollars), with a range of $188 to $565, three-injection protocol [641]
   - $200 (2002 US dollars), with a range of $200 to $600, three-injection protocol[642]

2. Booster shot protocol as seen in the literature.
   - Frequency
     - Every 10 years[643,644,645,646]
     - None required[647]
   - Cost $100 (2001 US dollars)[648,649]

Most researchers pursuing vaccination models have used an estimate of $300, with a booster shot required after 10 years at a cost of $100.

As a comparison, Canadian data for hepatitis C programs suggests that the cost of vaccination to be $184 (2003 CDN dollars), with a range used in sensitivity analysis of $25 to $300; this includes three injections and administration costs. [650]

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[639] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases.* 2003; 9(1): 37-48.
[640] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerging Infectious Diseases.* 2004; 10(11): 1915-23.
[641] Goldie SJ, Kohli M, Grima D et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute.* 2004; 96(8): 604-15.
[642] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *Journal of the American Medical Association.* 2003; 290(6): 781-9.
[643] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases.* 2003; 9(1): 37-48.
[644] Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology.* 2002; 13(6): 631-9.
[645] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerging Infectious Diseases.* 2004; 10(11): 1915-23.
[646] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *Journal of the American Medical Association.* 2003; 290(6): 781-9.
[647] Goldie SJ, Grima D, Kohli M et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *International Journal of Cancer*. 2003; 106(6): 896-904.
[648] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases.* 2003; 9(1): 37-48.
[649] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerging Infectious Diseases.* 2004; 10(11): 1915-23.

For this study, we have followed the lead established by other models and used a base estimate of $300, with a booster shot required at 10 years at a cost of $100. These costs will be varied in a subsequent sensitivity analysis. An additional assumption is that 80% of male and female 12 year olds will receive the vaccination. These factors enable us to generate the following table, which is dependent on B.C. population projections until 2031.

Estimating the Cost of a Vaccination Program
In Constant 2005 Canadian Dollars

	12 Year Old		Uptake (80%)		Costs - Females			Costs - Males		
Year	F	M	F	M	Original	Booster	**Total**	Original	Booster	**Total**
1	24,574	26,125	19,659	20,900	$ 5,897,760		**$ 5,897,760**	$ 6,270,000		**$ 6,270,000**
2	24,583	26,355	19,666	21,084	$ 5,899,920		**$ 5,899,920**	$ 6,325,200		**$ 6,325,200**
3	24,521	25,935	19,617	20,748	$ 5,885,040		**$ 5,885,040**	$ 6,224,400		**$ 6,224,400**
4	23,666	25,105	18,933	20,084	$ 5,679,840		**$ 5,679,840**	$ 6,025,200		**$ 6,025,200**
5	23,128	24,280	18,502	19,424	$ 5,550,720		**$ 5,550,720**	$ 5,827,200		**$ 5,827,200**
6	22,815	24,094	18,252	19,275	$ 5,475,600		**$ 5,475,600**	$ 5,782,560		**$ 5,782,560**
7	22,608	23,904	18,086	19,123	$ 5,425,920		**$ 5,425,920**	$ 5,736,960		**$ 5,736,960**
8	22,168	23,683	17,734	18,946	$ 5,320,320		**$ 5,320,320**	$ 5,683,920		**$ 5,683,920**
9	22,225	23,611	17,780	18,889	$ 5,334,000		**$ 5,334,000**	$ 5,666,640		**$ 5,666,640**
10	22,269	23,700	17,815	18,960	$ 5,344,560	$ 1,965,920	**$ 7,310,480**	$ 5,688,000	$ 2,090,000	**$ 7,778,000**
11	22,575	23,898	18,060	19,118	$ 5,418,000	$ 1,966,640	**$ 7,384,640**	$ 5,735,520	$ 2,108,400	**$ 7,843,920**
12	22,738	24,067	18,190	19,254	$ 5,457,120	$ 1,961,680	**$ 7,418,800**	$ 5,776,080	$ 2,074,800	**$ 7,850,880**
13	22,922	24,258	18,338	19,406	$ 5,501,280	$ 1,893,280	**$ 7,394,560**	$ 5,821,920	$ 2,008,400	**$ 7,830,320**
14	23,196	24,551	18,557	19,641	$ 5,567,040	$ 1,850,240	**$ 7,417,280**	$ 5,892,240	$ 1,942,400	**$ 7,834,640**
15	23,469	24,825	18,775	19,860	$ 5,632,560	$ 1,825,200	**$ 7,457,760**	$ 5,958,000	$ 1,927,520	**$ 7,885,520**
16	23,755	25,133	19,004	20,106	$ 5,701,200	$ 1,808,640	**$ 7,509,840**	$ 6,031,920	$ 1,912,320	**$ 7,944,240**
17	24,051	25,445	19,241	20,356	$ 5,772,240	$ 1,773,440	**$ 7,545,680**	$ 6,106,800	$ 1,894,640	**$ 8,001,440**
18	24,341	25,755	19,473	20,604	$ 5,841,840	$ 1,778,000	**$ 7,619,840**	$ 6,181,200	$ 1,888,880	**$ 8,070,080**
19	24,679	26,106	19,743	20,885	$ 5,922,960	$ 1,781,520	**$ 7,704,480**	$ 6,265,440	$ 1,896,000	**$ 8,161,440**
20	25,004	26,444	20,003	21,155	$ 6,000,960	$ 1,806,000	**$ 7,806,960**	$ 6,346,560	$ 1,911,840	**$ 8,258,400**
21	25,318	26,780	20,254	21,424	$ 6,076,320	$ 1,819,040	**$ 7,895,360**	$ 6,427,200	$ 1,925,360	**$ 8,352,560**
22	25,586	27,056	20,469	21,645	$ 6,140,640	$ 1,833,760	**$ 7,974,400**	$ 6,493,440	$ 1,940,640	**$ 8,434,080**
23	25,801	27,286	20,641	21,829	$ 6,192,240	$ 1,855,680	**$ 8,047,920**	$ 6,548,640	$ 1,964,080	**$ 8,512,720**
24	25,987	27,476	20,790	21,981	$ 6,236,880	$ 1,877,520	**$ 8,114,400**	$ 6,594,240	$ 1,986,000	**$ 8,580,240**
25	26,112	27,604	20,890	22,083	$ 6,266,880	$ 1,900,400	**$ 8,167,280**	$ 6,624,960	$ 2,010,640	**$ 8,635,600**
26	26,203	27,702	20,962	22,162	$ 6,288,720	$ 1,924,080	**$ 8,212,800**	$ 6,648,480	$ 2,035,600	**$ 8,684,080**

Assumptions:

Cost per Vaccination	$ 300
Cost per Booster Shot	$ 100

Over the quarter century of the program, the annual cost rises from about $12 million to almost $17 million (in constant 2005 CDN dollars). Of course, the biggest jump in costs comes in the year when the booster shot is first administered.

[650] Krahn MD, John-Baptiste A, Yi Q et al. Potential cost-effectiveness of a preventive hepatitis C vaccine in high risk and average risk populations in Canada. *Vaccine.* 2005; 23(13): 1549-58.

Clinical Impact of an HPV Vaccine

After costs have been established, the other major half of a health economic analysis needs to be brought in, namely, clinical effectiveness. Again, the assumptions and prevailing inputs need to be clearly identified. These include the following:

- The vaccine will target HPV 16/18/6/11.
- It will be administered to male and female 12 year olds.
- Following the best results from trials to date, the vaccine will be 100% efficacious.
- Booster shot required at 10 years, with no waning of efficacy during the interim.
- As indicated earlier, the model will run from 2006 to 2031 (i.e., the next 26 years).
- The incidence rates used in the model are summarized on the following table.

Incidence Rates Used in Model

Females

Age Group	Mild Atypia	Moderate or Higher Atypia	Cancers: Cervix	Vulva	Vagina	Anus	Tonsil	Nasal	Larynx	Genital Warts	RRP
13-14	-	-	-	-	-	-	-	-	-	0.43	0.74
15-19	-	-	-	-	-	-	-	-	-	2.87	0.74
20-24	22.42	8.40	4.75	2.17	0.24	0.07	0.07	0.20	0.10	6.20	1.80
25-29	22.42	8.40	4.75	2.17	0.24	0.07	0.07	0.20	0.10	3.94	1.80
30-34	18.16	4.97	10.76	2.17	0.24	0.07	0.07	0.20	0.10	2.65	1.80
35-39	18.16	4.97	10.76	2.17	0.24	0.07	0.07	0.20	0.10	1.99	1.80
Rate Per	*1,000*	*1,000*	*100,000*	*100,000*	*100,000*	*100,000*	*100,000*	*100,000*	*100,000*	*1,000*	*100,000*

Males

Age Group	Cancers: Penis	Anus	Tonsil	Nasal	Larynx	Genital Warts	RRP
13-14	-	-	-	-	-	0.41	0.74
15-19	-	-	-	-	-	0.65	0.74
20-24	0.47	0.17	0.14	0.10	0.17	2.93	1.80
25-29	0.47	0.17	0.14	0.10	0.17	5.01	1.80
30-34	0.47	0.17	0.14	0.10	0.17	3.88	1.80
35-39	0.47	0.17	0.14	0.10	0.17	2.52	1.80
Rate Per	*100,000*	*100,000*	*100,000*	*100,000*	*100,000*	*1,000*	*100,000*

The key outcome that needs to be tracked is the projected number of cases that will be avoided if the vaccine program is implemented according to the various assumptions delineated. The following two tables identify this data for females and males; the figures basically represent the subset of disease which would have been generated by the targeted viral infections, but which now is eliminated from the population. For example, the absence of HPV 16/18/6/11 in 80% of 12 year olds will avoid about 2 cervical cancer cases in the eleventh year of the program. The number of avoided cases in B.C. will grow to over 16 per year by the end of the program, this represents the latency effect, or the pattern where disease tends to develop only after persistent infection for years or even decades.

Potential Cases Avoided in British Columbia
Females Vaccinated against HPV 16/18/6/11

Year	Mild Atypia	Moderate or Higher Atypia	Malignant Diseases: Cervix	Vulva	Vagina	Anus	Tonsil	Nasal	Larynx	Non-Malignant Diseases: Genital Warts	RRP
1	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	8	0.11
3	-	-	-	-	-	-	-	-	-	15	0.22
4	-	-	-	-	-	-	-	-	-	66	0.33
5	-	-	-	-	-	-	-	-	-	116	0.44
6	-	-	-	-	-	-	-	-	-	167	0.54
7	-	-	-	-	-	-	-	-	-	215	0.64
8	-	-	-	-	-	-	-	-	-	263	0.90
9	291	109	0.62	0.43	0.04	0.01	0.01	0.04	0.01	369	1.16
10	582	218	1.23	0.85	0.07	0.02	0.02	0.08	0.03	474	1.42
11	872	327	1.85	1.28	0.11	0.03	0.03	0.12	0.04	579	1.67
12	1,152	432	2.44	1.69	0.15	0.04	0.03	0.16	0.05	682	1.92
13	1,426	534	3.02	2.09	0.18	0.05	0.04	0.20	0.06	783	2.17
14	1,696	636	3.59	2.49	0.22	0.06	0.05	0.23	0.08	845	2.42
15	1,964	736	4.16	2.88	0.25	0.07	0.06	0.27	0.09	906	2.67
16	2,226	834	4.71	3.26	0.28	0.08	0.07	0.31	0.10	967	2.92
17	2,490	933	5.27	3.65	0.32	0.09	0.08	0.34	0.11	1,030	3.17
18	2,753	1,032	5.83	4.04	0.35	0.10	0.08	0.38	0.13	1,094	3.42
19	2,965	1,087	7.17	4.43	0.38	0.11	0.09	0.41	0.14	1,138	3.68
20	3,179	1,144	8.52	4.82	0.42	0.12	0.10	0.45	0.15	1,183	3.94
21	3,395	1,201	9.88	5.22	0.45	0.13	0.11	0.49	0.16	1,229	4.20
22	3,617	1,261	11.21	5.62	0.49	0.14	0.12	0.53	0.17	1,278	4.46
23	3,843	1,323	12.53	6.03	0.52	0.15	0.12	0.56	0.19	1,328	4.73
24	4,072	1,387	13.85	6.44	0.56	0.16	0.13	0.60	0.20	1,368	5.00
25	4,306	1,453	15.17	6.86	0.59	0.17	0.14	0.64	0.21	1,409	5.28
26	4,545	1,521	16.48	7.28	0.63	0.18	0.15	0.68	0.23	1,451	5.55

Potential Cases Avoided in British Columbia
Males Vaccinated against HPV 16/18/6/11

Year	Malignant Diseases: Penis	Anus	Tonsil	Nasal	Larynx	Non-Malignant Diseases: Genital Warts	RRP
1	-	-	-	-	-	-	-
2	-	-	-	-	-	8	0.12
3	-	-	-	-	-	15	0.24
4	-	-	-	-	-	28	0.35
5	-	-	-	-	-	40	0.47
6	-	-	-	-	-	51	0.57
7	-	-	-	-	-	63	0.68
8	-	-	-	-	-	74	0.96
9	0.07	0.03	0.02	0.02	0.02	128	1.24
10	0.14	0.06	0.04	0.04	0.05	182	1.51
11	0.21	0.08	0.06	0.06	0.07	236	1.78
12	0.28	0.11	0.07	0.08	0.09	288	2.04
13	0.34	0.14	0.09	0.10	0.11	339	2.31
14	0.41	0.16	0.11	0.12	0.13	429	2.57
15	0.47	0.19	0.13	0.14	0.16	520	2.83
16	0.54	0.21	0.14	0.16	0.18	609	3.10
17	0.60	0.24	0.16	0.18	0.20	697	3.36
18	0.66	0.27	0.18	0.20	0.22	784	3.63
19	0.73	0.29	0.19	0.22	0.24	850	3.90
20	0.79	0.32	0.21	0.24	0.26	916	4.17
21	0.86	0.34	0.23	0.26	0.28	982	4.45
22	0.92	0.37	0.24	0.28	0.30	1,050	4.73
23	0.99	0.40	0.26	0.30	0.33	1,119	5.02
24	1.06	0.42	0.28	0.32	0.35	1,164	5.30
25	1.13	0.45	0.30	0.34	0.37	1,209	5.59
26	1.19	0.48	0.32	0.36	0.39	1,256	5.88

Potential Costs Avoided

Relating the avoided cases to the cost per case for each disease provides a simple formula for potential total costs avoided through a vaccination program. The estimated costs of treating HPV related diseases in B.C. in 2005 are summarized on the following table (see Appendix B for details).

Estimated Cost of Treating HPV related Diseases in BC in 2005

	Cost / Case Procedure
Cervical Cancer	
Conventional Cytology	$ 40
Mild Atypia	$ 13
Mild to Moderate Atypia (Precancers)	$ 984
Local Invasive Cervical Cancer	$ 11,716
Regional Invasive Cervical Cancer	$ 23,749
Distant Invasive Cervical Cancer	$ 35,979
Anogenital Cancers	
Vulva	$ 31,139
Vagina	$ 37,787
Penis	$ 37,787
Anus	$ 44,434
Cancers of the Head and Neck	
Tonsils	$ 26,103
Larynx	$ 47,912
Sinonasal	$ 63,599
Oral	$ 63,418
Non-Malignant Diseases	
Genital Warts	$ 549
Recurrent Respiratory Papillomatosis	
Children	$ 143,827
Adults	$ 100,679

The next two tables apply these costs per case / procedure to the estimated avoided cases and thus provide an estimate of avoided costs in females and males over the 26 years of the program. No attempt has been made to discount costs or outcomes.

For females, the estimated costs avoided begin at $28,000 in the second year of the program, increasing to $3.7 million in the final year of the model.

Potential Costs Avoided in British Columbia
Females Vaccinated with HPV 16/18/6/11

Year	Mild Atypia	Moderate or Higher Atypia	Malignant Diseases: Cervix	Vulva	Vagina	Anus	Tonsil	Nasal	Larynx	Non-Malignant Diseases: Genital Warts	RRP	Total
1	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	**$ -**
2	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,177	$ 11,131	**$ 15,308**
3	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 8,355	$ 22,267	**$ 30,622**
4	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 36,224	$ 33,374	**$ 69,599**
5	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 63,957	$ 44,094	**$ 108,051**
6	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 91,538	$ 54,571	**$ 146,109**
7	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 118,241	$ 64,905	**$ 183,147**
8	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 144,390	$ 91,091	**$ 235,482**
9	$ 3,923	$ 107,292	$ 14,668	$ 13,284	$ 1,396	$ 475	$ 230	$ 2,538	$ 634	$ 202,509	$ 117,084	**$ 464,033**
10	$ 7,847	$ 214,623	$ 29,341	$ 26,573	$ 2,793	$ 951	$ 461	$ 5,077	$ 1,268	$ 260,450	$ 143,062	**$ 692,446**
11	$ 11,761	$ 321,684	$ 43,977	$ 39,828	$ 4,186	$ 1,425	$ 691	$ 7,610	$ 1,901	$ 317,892	$ 168,505	**$ 919,460**
12	$ 15,539	$ 425,011	$ 58,103	$ 52,622	$ 5,530	$ 1,882	$ 912	$ 10,054	$ 2,512	$ 374,316	$ 193,737	**$ 1,140,220**
13	$ 19,231	$ 525,990	$ 71,908	$ 65,124	$ 6,844	$ 2,330	$ 1,129	$ 12,443	$ 3,109	$ 430,102	$ 218,841	**$ 1,357,050**
14	$ 22,872	$ 625,602	$ 85,526	$ 77,457	$ 8,141	$ 2,771	$ 1,343	$ 14,799	$ 3,697	$ 463,850	$ 243,893	**$ 1,549,952**
15	$ 26,481	$ 724,310	$ 99,021	$ 89,678	$ 9,425	$ 3,208	$ 1,555	$ 17,134	$ 4,281	$ 497,520	$ 268,784	**$ 1,741,398**
16	$ 30,020	$ 821,098	$ 112,252	$ 101,662	$ 10,685	$ 3,637	$ 1,763	$ 19,424	$ 4,853	$ 530,891	$ 293,836	**$ 1,930,119**
17	$ 33,568	$ 918,134	$ 125,518	$ 113,676	$ 11,947	$ 4,066	$ 1,971	$ 21,720	$ 5,426	$ 565,414	$ 319,046	**$ 2,120,485**
18	$ 37,122	$ 1,015,362	$ 138,810	$ 125,714	$ 13,212	$ 4,497	$ 2,180	$ 24,020	$ 6,001	$ 600,789	$ 344,588	**$ 2,312,295**
19	$ 39,981	$ 1,070,154	$ 170,851	$ 137,917	$ 14,495	$ 4,934	$ 2,391	$ 26,351	$ 6,583	$ 624,640	$ 370,368	**$ 2,468,665**
20	$ 42,865	$ 1,125,641	$ 202,995	$ 150,209	$ 15,787	$ 5,373	$ 2,604	$ 28,700	$ 7,170	$ 649,230	$ 396,420	**$ 2,626,994**
21	$ 45,780	$ 1,182,043	$ 235,203	$ 162,600	$ 17,089	$ 5,817	$ 2,819	$ 31,067	$ 7,761	$ 674,821	$ 422,797	**$ 2,787,796**
22	$ 48,765	$ 1,241,163	$ 266,928	$ 175,139	$ 18,407	$ 6,265	$ 3,036	$ 33,463	$ 8,360	$ 701,537	$ 449,493	**$ 2,952,557**
23	$ 51,809	$ 1,302,434	$ 298,409	$ 187,826	$ 19,740	$ 6,719	$ 3,256	$ 35,887	$ 8,966	$ 729,207	$ 476,497	**$ 3,120,751**
24	$ 54,909	$ 1,365,511	$ 329,825	$ 200,667	$ 21,090	$ 7,178	$ 3,479	$ 38,341	$ 9,579	$ 751,068	$ 503,789	**$ 3,285,437**
25	$ 58,063	$ 1,430,249	$ 361,261	$ 213,669	$ 22,456	$ 7,643	$ 3,704	$ 40,825	$ 10,199	$ 773,566	$ 531,355	**$ 3,452,991**
26	$ 61,276	$ 1,497,037	$ 392,538	$ 226,827	$ 23,839	$ 8,114	$ 3,933	$ 43,339	$ 10,827	$ 796,751	$ 559,196	**$ 3,623,677**

The most significant avoided costs are for precancerous conditions of the cervix and for non-malignant diseases; by the end of the 26 years, cervical atypia and cervical cancers make up 54% of all costs avoided annually, while genital warts and recurrent respiratory papillomatosis make up another 37%.

For males, the estimated costs avoided begin at about $20,000 in the second year of the program, increasing to almost $1.6 million in the final year of the model.

Potential Costs Avoided in British Columbia
Males Vaccinated with HPV 16/18/6/11

	Malignant Diseases					Non-Malignant Diseases		
Year	Penis	Anus	Tonsil	Nasal	Larynx	Genital Warts	RRP	**Total**
1	$ -	$ -	$ -	$ -	$ -	$ -	$ -	**$ -**
2	$ -	$ -	$ -	$ -	$ -	$ 4,234	$ 11,834	**$ 16,068**
3	$ -	$ -	$ -	$ -	$ -	$ 8,505	$ 23,772	**$ 32,277**
4	$ -	$ -	$ -	$ -	$ -	$ 15,187	$ 35,520	**$ 50,707**
5	$ -	$ -	$ -	$ -	$ -	$ 21,756	$ 46,892	**$ 68,648**
6	$ -	$ -	$ -	$ -	$ -	$ 28,151	$ 57,890	**$ 86,041**
7	$ -	$ -	$ -	$ -	$ -	$ 34,437	$ 68,804	**$ 103,242**
8	$ -	$ -	$ -	$ -	$ -	$ 40,615	$ 96,583	**$ 137,198**
9	$ 2,652	$ 1,248	$ 486	$ 1,343	$ 1,110	$ 70,283	$ 124,412	**$ 201,535**
10	$ 5,328	$ 2,507	$ 976	$ 2,697	$ 2,230	$ 100,130	$ 151,935	**$ 265,804**
11	$ 7,961	$ 3,746	$ 1,459	$ 4,030	$ 3,333	$ 129,591	$ 178,960	**$ 329,079**
12	$ 10,509	$ 4,946	$ 1,926	$ 5,320	$ 4,400	$ 158,330	$ 205,540	**$ 390,969**
13	$ 12,974	$ 6,106	$ 2,378	$ 6,567	$ 5,431	$ 186,360	$ 232,075	**$ 451,892**
14	$ 15,420	$ 7,257	$ 2,826	$ 7,806	$ 6,455	$ 235,753	$ 258,573	**$ 534,090**
15	$ 17,847	$ 8,399	$ 3,271	$ 9,034	$ 7,471	$ 285,227	$ 285,061	**$ 616,310**
16	$ 20,251	$ 9,530	$ 3,712	$ 10,251	$ 8,478	$ 334,219	$ 311,626	**$ 698,067**
17	$ 22,648	$ 10,658	$ 4,151	$ 11,464	$ 9,481	$ 382,541	$ 338,389	**$ 779,333**
18	$ 25,054	$ 11,791	$ 4,592	$ 12,682	$ 10,489	$ 430,342	$ 365,421	**$ 860,370**
19	$ 27,480	$ 12,932	$ 5,037	$ 13,910	$ 11,504	$ 466,578	$ 392,704	**$ 930,145**
20	$ 29,923	$ 14,082	$ 5,484	$ 15,147	$ 12,527	$ 502,795	$ 420,269	**$ 1,000,227**
21	$ 32,386	$ 15,241	$ 5,936	$ 16,394	$ 13,558	$ 539,273	$ 448,178	**$ 1,070,965**
22	$ 34,878	$ 16,414	$ 6,392	$ 17,655	$ 14,602	$ 576,415	$ 476,416	**$ 1,142,773**
23	$ 37,398	$ 17,600	$ 6,854	$ 18,931	$ 15,657	$ 614,323	$ 504,979	**$ 1,215,742**
24	$ 39,950	$ 18,801	$ 7,322	$ 20,222	$ 16,725	$ 638,778	$ 533,849	**$ 1,275,648**
25	$ 42,533	$ 20,016	$ 7,795	$ 21,530	$ 17,806	$ 663,672	$ 563,007	**$ 1,336,360**
26	$ 45,147	$ 21,247	$ 8,275	$ 22,853	$ 18,901	$ 689,370	$ 592,450	**$ 1,398,243**

The costs avoided for males are much smaller, almost wholly accounted for by ruling out the categories involving cervical disease. Genital warts and RRP rank very high for males, accounting for fully 92% of potential costs avoided annually by the end of 26 years. The clear predominance of male cases in tonsillar and laryngeal cancer, as described in an earlier section of this report, is borne out by the higher costs avoided with these diseases compared with females. The fact that men are overtaking women in anal cancer incidence is also reflected in the financial data, indicating that men have increasingly more to gain from a vaccine with regard to this type of malignancy.

Having compared the separate results for males and females, we now combine the figures to estimate the total annual costs avoided with a quadrivalent HPV vaccine in B.C. during the 26 year program (see the following table).

Potential Costs Avoided in British Columbia
Annual Vaccination of 12 Year Olds
With HPV 16/18/6/11 Vaccine

Year	Females	Males	**Total**
1	$ -	$ -	**$ -**
2	$ 15,308	$ 16,068	**$ 31,376**
3	$ 30,622	$ 32,277	**$ 62,899**
4	$ 69,599	$ 50,707	**$ 120,305**
5	$ 108,051	$ 68,648	**$ 176,699**
6	$ 146,109	$ 86,041	**$ 232,150**
7	$ 183,147	$ 103,242	**$ 286,388**
8	$ 235,482	$ 137,198	**$ 372,680**
9	$ 464,033	$ 201,535	**$ 665,568**
10	$ 692,446	$ 265,804	**$ 958,249**
11	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 3,623,677	$ 1,398,243	**$ 5,021,920**

The total estimated costs avoided begin at $31,000 in the second year of the program, increasing to $5.0 million in the final year of the model.

Summary

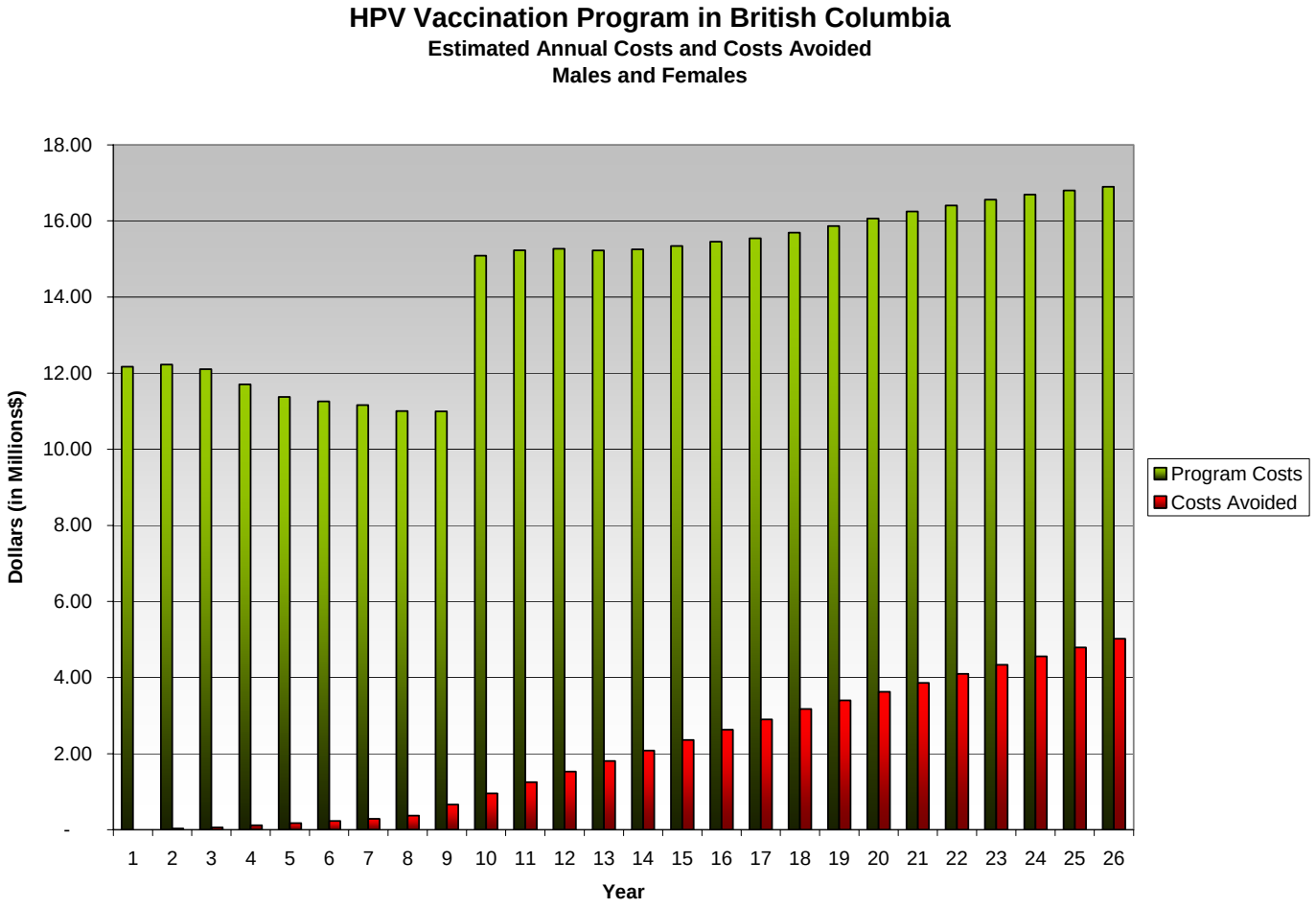
The following table pulls together the costs and effectiveness (as represented by avoided costs) of a vaccination program in B.C.

HPV Vaccination Program in British Columbia
Estimated Annual Costs and Cost Avoided
With HPV 16/18/6/11 Vaccine
(In Constant 2005 Canadian Dollars)

	Estimated Vaccination Program Costs			Potential Medical Costs Avoided		
Year	Females	Males	**Total**	Females	Males	**Total**
1	$ 5,897,760	$ 6,270,000	**$ 12,167,760**	$ -	$ -	**$ -**
2	$ 5,899,920	$ 6,325,200	**$ 12,225,120**	$ 15,308	$ 16,068	**$ 31,376**
3	$ 5,885,040	$ 6,224,400	**$ 12,109,440**	$ 30,622	$ 32,277	**$ 62,899**
4	$ 5,679,840	$ 6,025,200	**$ 11,705,040**	$ 69,599	$ 50,707	**$ 120,305**
5	$ 5,550,720	$ 5,827,200	**$ 11,377,920**	$ 108,051	$ 68,648	**$ 176,699**
6	$ 5,475,600	$ 5,782,560	**$ 11,258,160**	$ 146,109	$ 86,041	**$ 232,150**
7	$ 5,425,920	$ 5,736,960	**$ 11,162,880**	$ 183,147	$ 103,242	**$ 286,388**
8	$ 5,320,320	$ 5,683,920	**$ 11,004,240**	$ 235,482	$ 137,198	**$ 372,680**
9	$ 5,334,000	$ 5,666,640	**$ 11,000,640**	$ 464,033	$ 201,535	**$ 665,568**
10	$ 7,310,480	$ 7,778,000	**$ 15,088,480**	$ 692,446	$ 265,804	**$ 958,249**
11	$ 7,384,640	$ 7,843,920	**$ 15,228,560**	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 7,418,800	$ 7,850,880	**$ 15,269,680**	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 7,394,560	$ 7,830,320	**$ 15,224,880**	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 7,417,280	$ 7,834,640	**$ 15,251,920**	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 7,457,760	$ 7,885,520	**$ 15,343,280**	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 7,509,840	$ 7,944,240	**$ 15,454,080**	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 7,545,680	$ 8,001,440	**$ 15,547,120**	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 7,619,840	$ 8,070,080	**$ 15,689,920**	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 7,704,480	$ 8,161,440	**$ 15,865,920**	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 7,806,960	$ 8,258,400	**$ 16,065,360**	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 7,895,360	$ 8,352,560	**$ 16,247,920**	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 7,974,400	$ 8,434,080	**$ 16,408,480**	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 8,047,920	$ 8,512,720	**$ 16,560,640**	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 8,114,400	$ 8,580,240	**$ 16,694,640**	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 8,167,280	$ 8,635,600	**$ 16,802,880**	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 8,212,800	$ 8,684,080	**$ 16,896,880**	$ 3,623,677	$ 1,398,243	**$ 5,021,920**
Total	**$ 181,451,600**	**$ 192,200,240**	**$ 373,651,840**	**$ 39,334,643**	**$ 14,991,731**	**$ 54,326,374**

It becomes quickly apparent that there is a wide gap between the expense of a vaccination program (under the assumptions we set in the beginning) and the direct medical costs avoided. The ratio of these two figures (expense : avoided cost) does improve, from 0.003 in year 2 to 0.297 in year 26, holding out hope that there might be a better financial balance over the projected lifetime of a 12 year old (though it is difficult to imagine even the undiscounted cumulative costs ever being "recovered"). In any event, no matter how favourable a 40 or 50 year projection might be, a quarter century is already a long time to assume static conditions in any model; it would be difficult to have confidence in longer projections.

The results presented in the preceding table are shown graphically on the following chart.



Sensitivity Analysis

The only significant analysis which remains is to see whether changing the key initial assumptions will have a vital effect on the financial profile of a vaccination program. Out of many possible scenarios, three sensitivity analyses will be performed, with the results offered first in tabular form and then graphically.

1. Change the cost of the initial vaccination from $300 to $100, and the cost of the booster shot from $100 to $25.

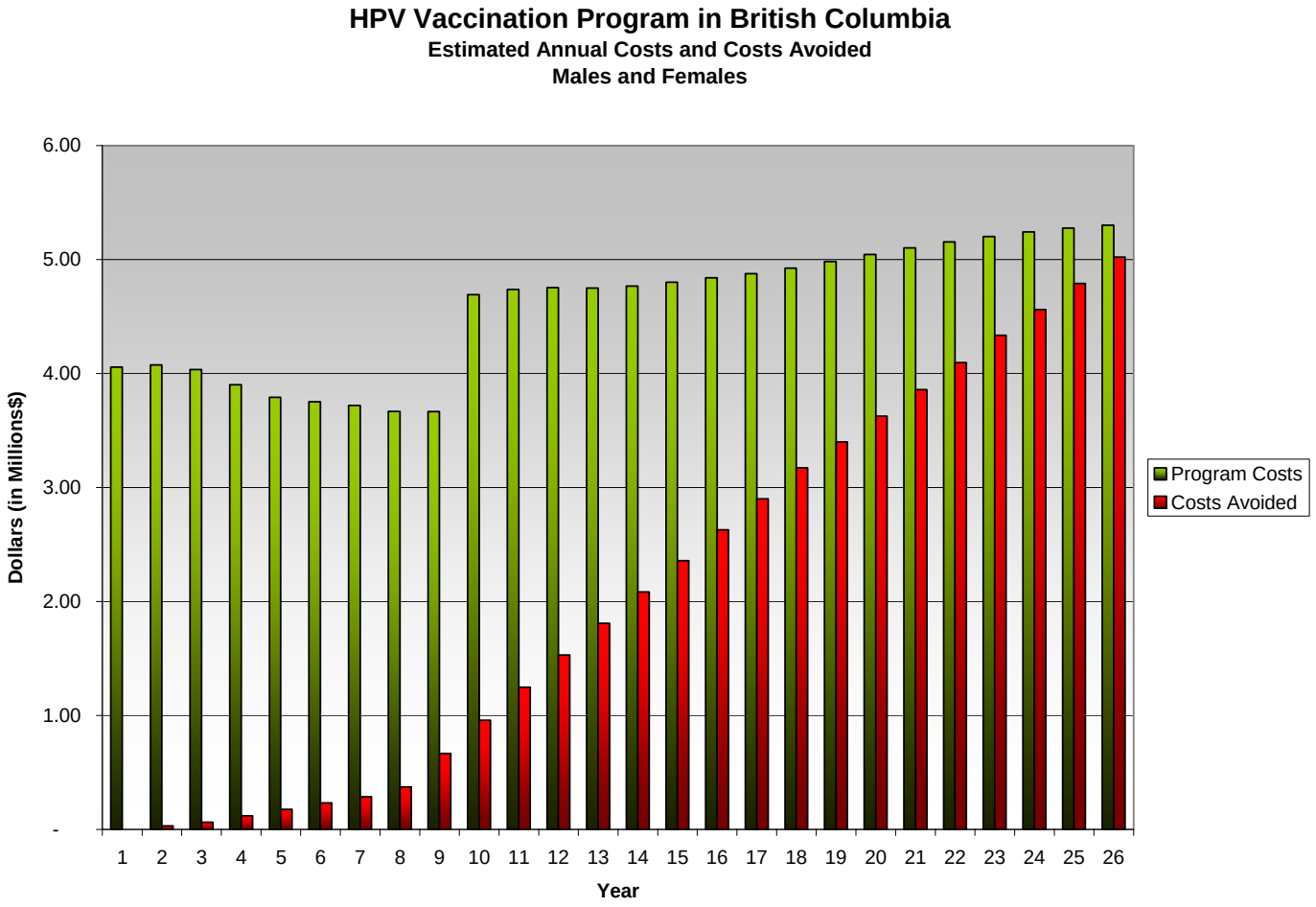
The results of this sensitivity analysis are indicated on the following table.

HPV Vaccination Program in British Columbia
Estimated Annual Costs and Cost Avoided
With HPV 16/18/6/11 Vaccine
(In Constant 2005 Canadian Dollars)

Year	Estimated Vaccination Program Costs			Potential Medical Costs Avoided		
	Females	Males	**Total**	Females	Males	**Total**
1	$ 1,965,920	$ 2,090,000	**$ 4,055,920**	$ -	$ -	**$ -**
2	$ 1,966,640	$ 2,108,400	**$ 4,075,040**	$ 15,308	$ 16,068	**$ 31,376**
3	$ 1,961,680	$ 2,074,800	**$ 4,036,480**	$ 30,622	$ 32,277	**$ 62,899**
4	$ 1,893,280	$ 2,008,400	**$ 3,901,680**	$ 69,599	$ 50,707	**$ 120,305**
5	$ 1,850,240	$ 1,942,400	**$ 3,792,640**	$ 108,051	$ 68,648	**$ 176,699**
6	$ 1,825,200	$ 1,927,520	**$ 3,752,720**	$ 146,109	$ 86,041	**$ 232,150**
7	$ 1,808,640	$ 1,912,320	**$ 3,720,960**	$ 183,147	$ 103,242	**$ 286,388**
8	$ 1,773,440	$ 1,894,640	**$ 3,668,080**	$ 235,482	$ 137,198	**$ 372,680**
9	$ 1,778,000	$ 1,888,880	**$ 3,666,880**	$ 464,033	$ 201,535	**$ 665,568**
10	$ 2,273,000	$ 2,418,500	**$ 4,691,500**	$ 692,446	$ 265,804	**$ 958,249**
11	$ 2,297,660	$ 2,438,940	**$ 4,736,600**	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 2,309,460	$ 2,444,060	**$ 4,753,520**	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 2,307,080	$ 2,442,740	**$ 4,749,820**	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 2,318,240	$ 2,449,680	**$ 4,767,920**	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 2,333,820	$ 2,467,880	**$ 4,801,700**	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 2,352,560	$ 2,488,720	**$ 4,841,280**	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 2,367,440	$ 2,509,260	**$ 4,876,700**	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 2,391,780	$ 2,532,620	**$ 4,924,400**	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 2,419,700	$ 2,562,480	**$ 4,982,180**	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 2,451,820	$ 2,593,480	**$ 5,045,300**	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 2,480,200	$ 2,623,740	**$ 5,103,940**	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 2,505,320	$ 2,649,640	**$ 5,154,960**	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 2,528,000	$ 2,673,900	**$ 5,201,900**	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 2,548,340	$ 2,694,580	**$ 5,242,920**	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 2,564,060	$ 2,710,980	**$ 5,275,040**	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 2,577,260	$ 2,725,060	**$ 5,302,320**	$ 3,623,677	$ 1,398,243	**$ 5,021,920**
Total	**$ 57,848,780**	**$ 61,273,620**	**$ 119,122,400**	**$ 39,334,643**	**$ 14,991,731**	**$ 54,326,374**

Over the 26 year time frame of the model, total vaccination program costs would decrease from $373.7 million to $119.1 million.

The results presented in the preceding table are shown graphically on the following chart.



The "bottom line" of this scenario is a much closer alignment between expenses and costs avoided by the end of the 26 year period of the model, but cumulative expenses are still well in front (by a factor of 2).

2. Change cost of vaccination to $45 and booster shot to $15.

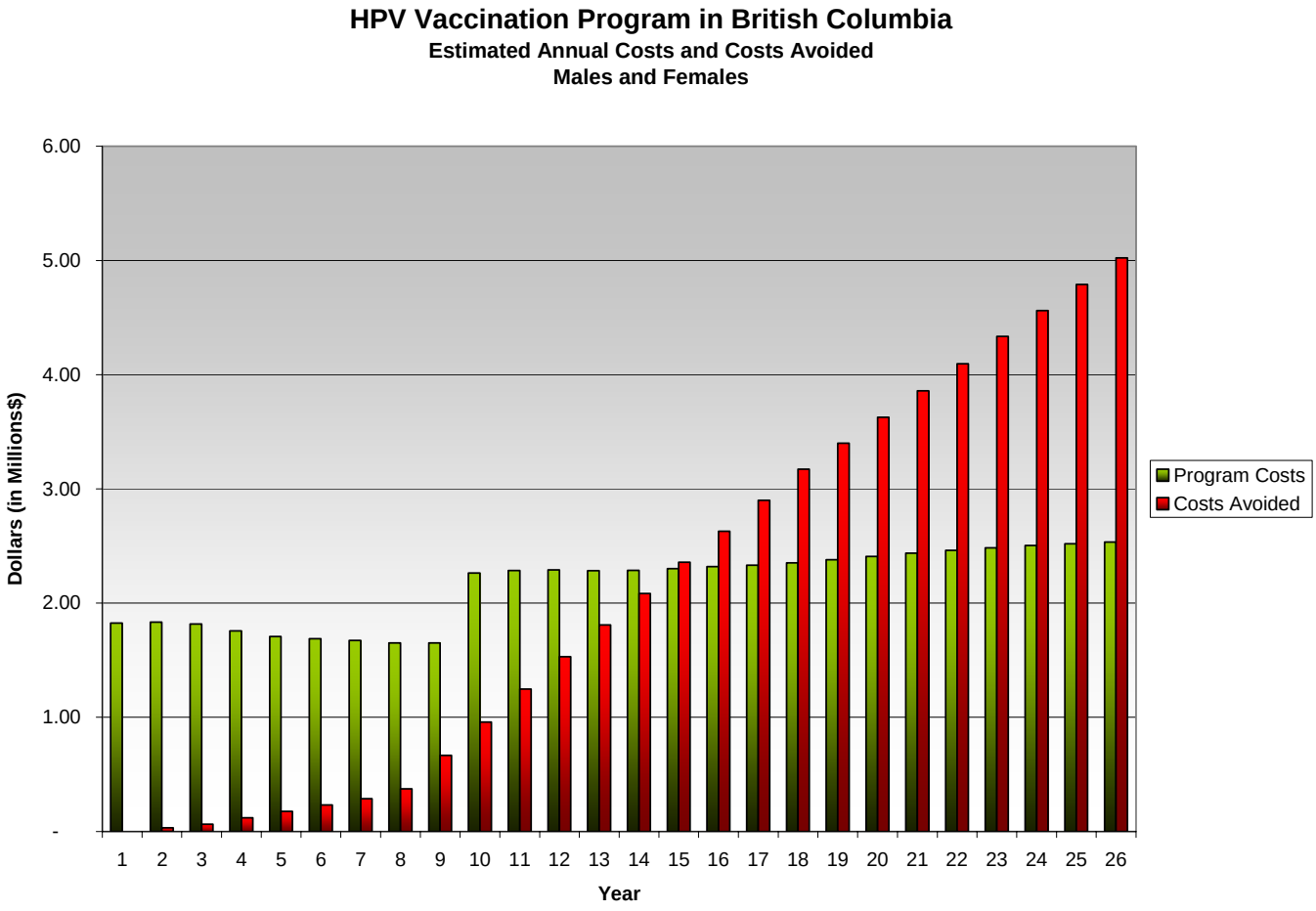
The results of this sensitivity analysis are indicated on the following table.

HPV Vaccination Program in British Columbia
Estimated Annual Costs and Cost Avoided
With HPV 16/18/6/11 Vaccine
(In Constant 2005 Canadian Dollars)

	Estimated Vaccination Program Costs			**Potential Medical Costs Avoided**		
Year	Females	Males	**Total**	Females	Males	**Total**
1	$ 884,664	$ 940,500	**$ 1,825,164**	$ -	$ -	**$ -**
2	$ 884,988	$ 948,780	**$ 1,833,768**	$ 15,308	$ 16,068	**$ 31,376**
3	$ 882,756	$ 933,660	**$ 1,816,416**	$ 30,622	$ 32,277	**$ 62,899**
4	$ 851,976	$ 903,780	**$ 1,755,756**	$ 69,599	$ 50,707	**$ 120,305**
5	$ 832,608	$ 874,080	**$ 1,706,688**	$ 108,051	$ 68,648	**$ 176,699**
6	$ 821,340	$ 867,384	**$ 1,688,724**	$ 146,109	$ 86,041	**$ 232,150**
7	$ 813,888	$ 860,544	**$ 1,674,432**	$ 183,147	$ 103,242	**$ 286,388**
8	$ 798,048	$ 852,588	**$ 1,650,636**	$ 235,482	$ 137,198	**$ 372,680**
9	$ 800,100	$ 849,996	**$ 1,650,096**	$ 464,033	$ 201,535	**$ 665,568**
10	$ 1,096,572	$ 1,166,700	**$ 2,263,272**	$ 692,446	$ 265,804	**$ 958,249**
11	$ 1,107,696	$ 1,176,588	**$ 2,284,284**	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 1,112,820	$ 1,177,632	**$ 2,290,452**	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 1,109,184	$ 1,174,548	**$ 2,283,732**	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 1,112,592	$ 1,175,196	**$ 2,287,788**	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 1,118,664	$ 1,182,828	**$ 2,301,492**	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 1,126,476	$ 1,191,636	**$ 2,318,112**	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 1,131,852	$ 1,200,216	**$ 2,332,068**	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 1,142,976	$ 1,210,512	**$ 2,353,488**	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 1,155,672	$ 1,224,216	**$ 2,379,888**	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 1,171,044	$ 1,238,760	**$ 2,409,804**	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 1,184,304	$ 1,252,884	**$ 2,437,188**	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 1,196,160	$ 1,265,112	**$ 2,461,272**	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 1,207,188	$ 1,276,908	**$ 2,484,096**	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 1,217,160	$ 1,287,036	**$ 2,504,196**	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 1,225,092	$ 1,295,340	**$ 2,520,432**	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 1,231,920	$ 1,302,612	**$ 2,534,532**	$ 3,623,677	$ 1,398,243	**$ 5,021,920**
Total	**$ 27,217,740**	**$ 28,830,036**	**$ 56,047,776**	**$ 39,334,643**	**$ 14,991,731**	**$ 54,326,374**

The vaccination and booster costs in this scenario were not chosen at random; they represent the amounts needed to approximately "zero out" the cumulative comparison of expenses and costs avoided over 26 years.

The results presented in the preceding table are shown graphically on the following chart.



The area of the two sets of bars in this graph are close to being equal, i.e., representing around $55 million.

3. Change the assumption of a three-injection protocol to a two-injection protocol with the cost decreasing from $300 to $200 for the initial vaccination and the cost of the booster shot costing $100.

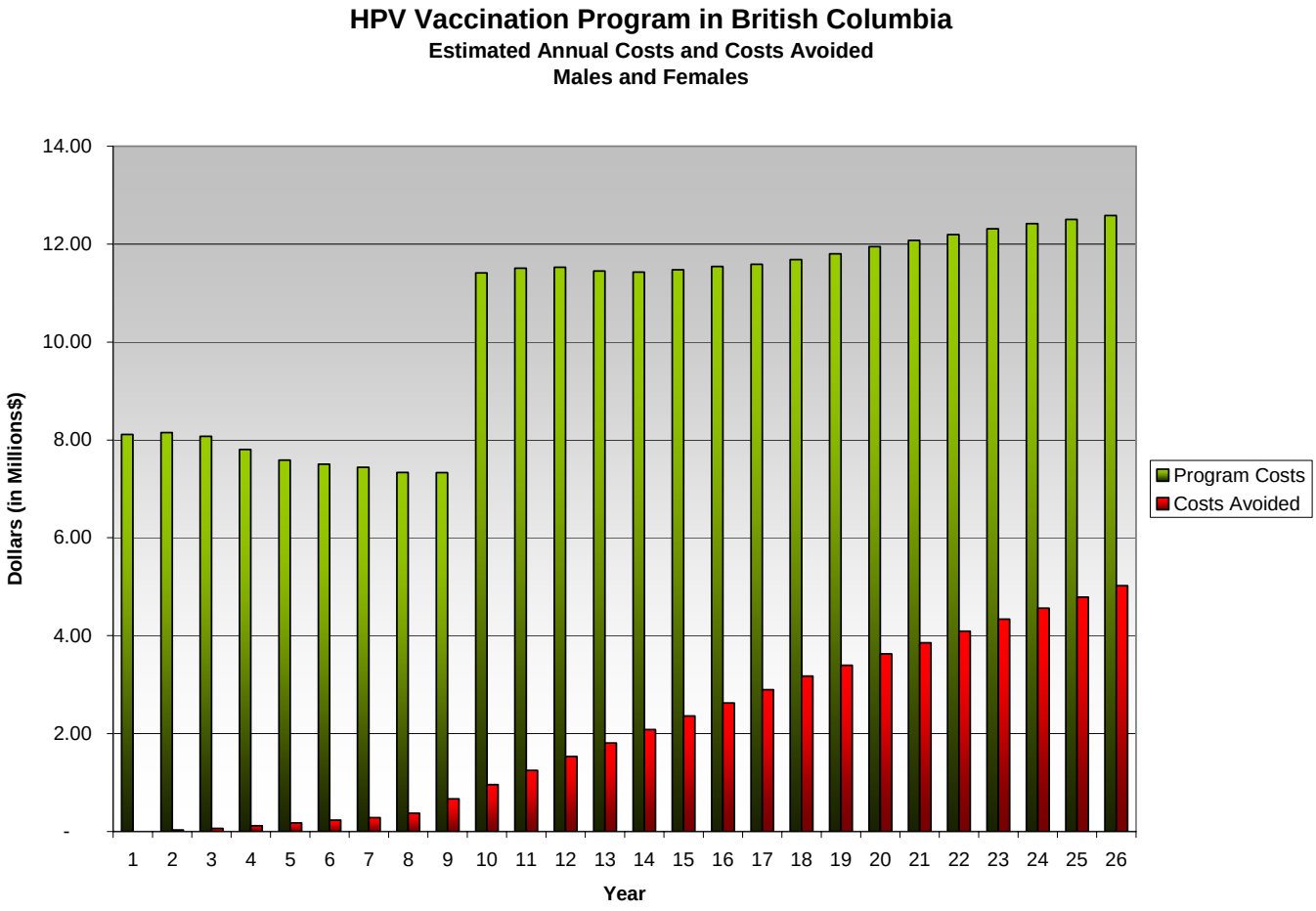
The results of this sensitivity analysis are indicated on the following table.

HPV Vaccination Program in British Columbia
Estimated Annual Costs and Cost Avoided
With HPV 16/18/6/11 Vaccine
(In Constant 2005 Canadian Dollars)

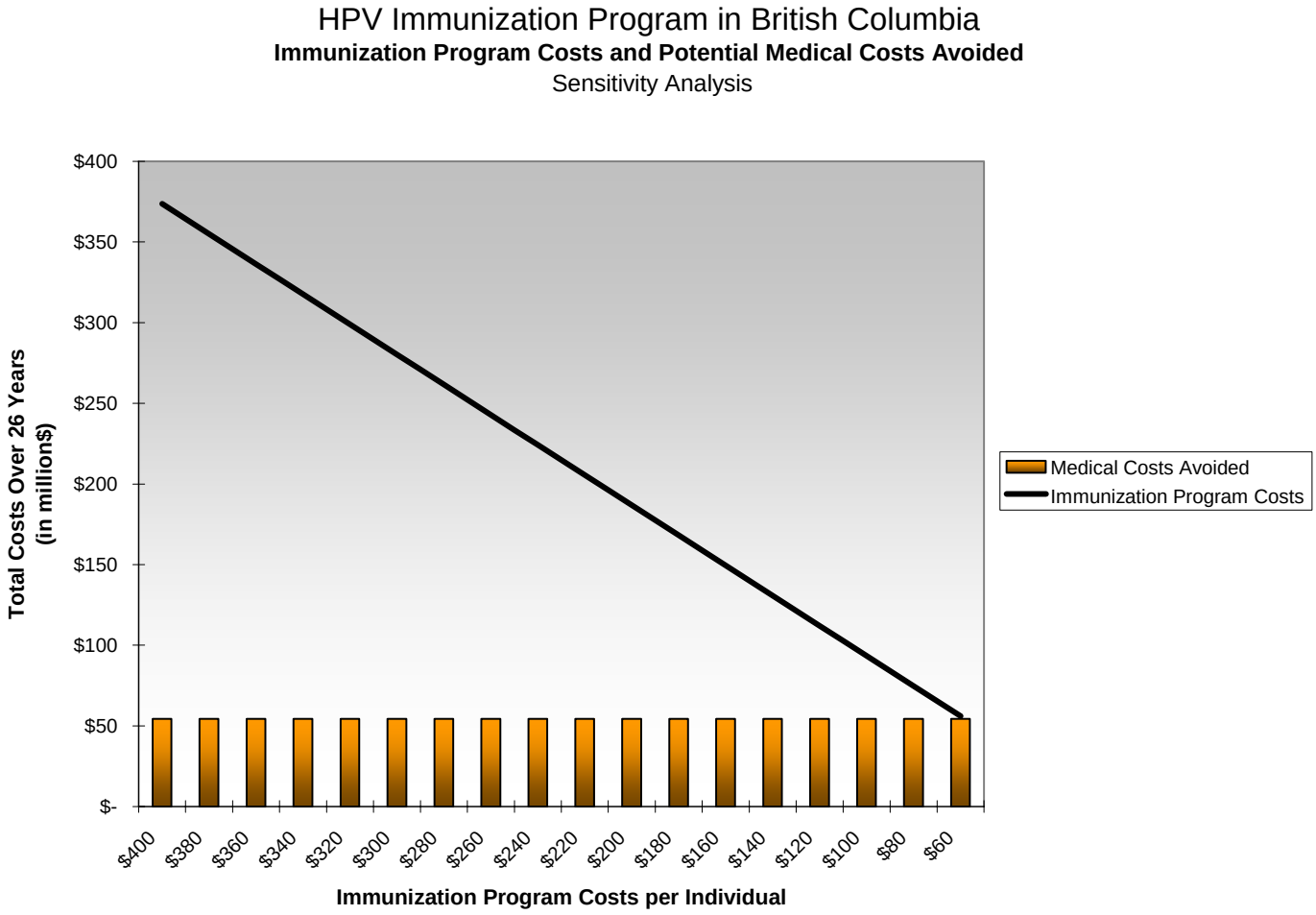
	Estimated Vaccination Program Costs			**Potential Medical Costs Avoided**		
Year	Females	Males	**Total**	Females	Males	**Total**
1	$ 3,931,840	$ 4,180,000	**$ 8,111,840**	$ -	$ -	**$ -**
2	$ 3,933,280	$ 4,216,800	**$ 8,150,080**	$ 15,308	$ 16,068	**$ 31,376**
3	$ 3,923,360	$ 4,149,600	**$ 8,072,960**	$ 30,622	$ 32,277	**$ 62,899**
4	$ 3,786,560	$ 4,016,800	**$ 7,803,360**	$ 69,599	$ 50,707	**$ 120,305**
5	$ 3,700,480	$ 3,884,800	**$ 7,585,280**	$ 108,051	$ 68,648	**$ 176,699**
6	$ 3,650,400	$ 3,855,040	**$ 7,505,440**	$ 146,109	$ 86,041	**$ 232,150**
7	$ 3,617,280	$ 3,824,640	**$ 7,441,920**	$ 183,147	$ 103,242	**$ 286,388**
8	$ 3,546,880	$ 3,789,280	**$ 7,336,160**	$ 235,482	$ 137,198	**$ 372,680**
9	$ 3,556,000	$ 3,777,760	**$ 7,333,760**	$ 464,033	$ 201,535	**$ 665,568**
10	$ 5,528,960	$ 5,882,000	**$ 11,410,960**	$ 692,446	$ 265,804	**$ 958,249**
11	$ 5,578,640	$ 5,932,080	**$ 11,510,720**	$ 919,460	$ 329,079	**$ 1,248,539**
12	$ 5,599,760	$ 5,925,520	**$ 11,525,280**	$ 1,140,220	$ 390,969	**$ 1,531,189**
13	$ 5,560,800	$ 5,889,680	**$ 11,450,480**	$ 1,357,050	$ 451,892	**$ 1,808,942**
14	$ 5,561,600	$ 5,870,560	**$ 11,432,160**	$ 1,549,952	$ 534,090	**$ 2,084,042**
15	$ 5,580,240	$ 5,899,520	**$ 11,479,760**	$ 1,741,398	$ 616,310	**$ 2,357,708**
16	$ 5,609,440	$ 5,933,600	**$ 11,543,040**	$ 1,930,119	$ 698,067	**$ 2,628,186**
17	$ 5,621,600	$ 5,965,840	**$ 11,587,440**	$ 2,120,485	$ 779,333	**$ 2,899,818**
18	$ 5,672,560	$ 6,009,680	**$ 11,682,240**	$ 2,312,295	$ 860,370	**$ 3,172,665**
19	$ 5,730,160	$ 6,072,960	**$ 11,803,120**	$ 2,468,665	$ 930,145	**$ 3,398,810**
20	$ 5,806,640	$ 6,142,880	**$ 11,949,520**	$ 2,626,994	$ 1,000,227	**$ 3,627,221**
21	$ 5,869,920	$ 6,210,160	**$ 12,080,080**	$ 2,787,796	$ 1,070,965	**$ 3,858,761**
22	$ 5,927,520	$ 6,269,600	**$ 12,197,120**	$ 2,952,557	$ 1,142,773	**$ 4,095,330**
23	$ 5,983,840	$ 6,329,840	**$ 12,313,680**	$ 3,120,751	$ 1,215,742	**$ 4,336,493**
24	$ 6,035,440	$ 6,382,160	**$ 12,417,600**	$ 3,285,437	$ 1,275,648	**$ 4,561,084**
25	$ 6,078,320	$ 6,427,280	**$ 12,505,600**	$ 3,452,991	$ 1,336,360	**$ 4,789,351**
26	$ 6,116,560	$ 6,467,920	**$ 12,584,480**	$ 3,623,677	$ 1,398,243	**$ 5,021,920**
Total	**$ 131,508,080**	**$ 139,306,000**	**$ 270,814,080**	**$ 39,334,643**	**$ 14,991,731**	**$ 54,326,374**

Over the 26 year time frame of the model, total vaccination program costs would decrease from $373.7 million to $270.8 million.

The results presented in the preceding table are shown graphically on the following chart.



In the preceding pages we have focused on three potential scenarios in which the costs of the HPV immunization program have been varied from $60 to $400. The following chart provides a summary comparison of the estimated total medical costs avoided ($54.3 million) over the 26 year time period from 2006 to 2031 in comparison to the total immunization program costs during the same time period if the cost per individual of the vaccinations is varied from $60 to $400.



From a strict medical cost perspective, the program 'breaks even' when immunization costs are reduced to $60 per individual.

Key Issues

It has become apparent in this report that evaluating the introduction of a vaccination program involves a complex set of factors and assumptions. While we have addressed and incorporated many of these, several issues and questions remain for ongoing consideration.

- What is the best setting for the program? School-based vaccination programs have a much higher success rate than those pursued in traditional health care settings.

- Targeting high risk groups may be more cost-effective, but these groups tend to be the hardest to reach. As well, the relevant risk factors may not be easy to detect.

- Why vaccinate 12 year old girls? A study by the US Centers for Disease Control indicated that 3% of girls have had sexual intercourse by age 13, 18.6% by age 15, and 59.2% by age 18. A reasonable goal may be to catch virtually all females before they have any sexual contact.

- Should both boys and girls be vaccinated? As we indicated earlier, some modelling has questioned the cost-effectiveness of extending HPV vaccines to males. However, it may be easier to have population acceptance if both males and females participate in a vaccination program.

- Will parental consent be required or will a vaccination program be part of public health policy? If parental consent is required, how many parents will agree to have their 12 year old daughters vaccinated against a sexually transmitted disease? And how can this proportion be increased through educational and other means?

- How might screening costs in the population be reasonably reduced over the course of a vaccination program?

- How will patterns of transmission and HPV infection change in the future, especially in the light of co-infections with viruses such as HIV?

- Is there an advantage to going beyond a quadrivalent vaccine and target even more types? What would this cost and how long would trials take?

- Women who are vaccinated would be expected to reduce their participation in screening programs, thus potentially offsetting some of the costs of the vaccination program. Some continued participation, but at less frequent intervals, would be expected and encouraged. What would the potential extent of savings due to reduced screening be?

Appendix A: Estimating the Impact of HPV Infection in British Columbia

New Cancer Cases in Britsh Columbia
Jan 1, 1999 to Dec 31, 2003

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
	M	F	M	F	M	F	M	F	M	F	M	F	Total
Vulva		4		64		208		114		63	-	453	*453*
Vagina		-		7		29		42		19	-	97	*97*
Anus	-	-	5	2	19	7	4	19	5	4	33	32	*65*
Penis	-		14		35		82		12		143	-	*143*
Conjunctiva	-	-	-	-	-	1	2	-	3	-	5	1	*6*
Oral Cavity	-	-	-	-	2	2	13	5	1	5	16	12	*28*
Tonsil	-	-	4	2	98	22	69	24	6	8	177	56	*233*
Nasal Cavity	-	1	3	6	16	14	18	21	8	13	45	55	*100*
Larynx	-	-	5	3	93	15	242	45	46	8	386	71	*457*

Population in Britsh Columbia
Jan 1, 1999 to Dec 31, 2003

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
	M	F	M	F	M	F	M	F	M	F	M	F	Total
1999	521,045	491,371	605,540	598,492	555,570	557,040	266,906	292,291	44,493	78,594	1,993,554	2,017,788	*4,011,342*
2000	518,849	489,164	597,834	591,851	571,315	574,869	271,137	294,696	46,896	82,587	2,006,031	2,033,167	*4,039,198*
2001	517,701	487,917	593,123	588,755	586,944	592,308	276,940	298,536	49,436	86,787	2,024,144	2,054,303	*4,078,447*
2002	513,461	484,831	589,840	586,868	602,291	608,909	282,642	302,882	52,217	91,040	2,040,451	2,074,530	*4,114,981*
2003	506,913	479,270	585,735	583,505	617,044	625,070	290,012	308,923	54,975	95,133	2,054,679	2,091,901	*4,146,580*
5 Year Total	**2,577,969**	**2,432,553**	**2,972,072**	**2,949,471**	**2,933,164**	**2,958,196**	**1,387,637**	**1,497,328**	**248,017**	**434,141**	**10,118,859**	**10,271,689**	**20,390,548**

New Cancer Cases in Britsh Columbia
Jan 1, 1999 to Dec 31, 2003
Annual Rate per 1,000,000

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
	M	F	M	F	M	F	M	F	M	F	M	F	Total
Vulva		1.6		21.7		70.3		76.1		145.1		**44.1**	
Vagina		-		2.4		9.8		28.0		43.8		**9.4**	
Anus	-	-	1.7	0.7	6.5	2.4	2.9	12.7	20.2	9.2	**3.3**	**3.1**	**3.2**
Penis	-		4.7		11.9		59.1		48.4		**14.1**		
Conjunctiva	-	-	-	-	-	0.3	1.4	-	12.1	-	**0.5**	**0.1**	**0.3**
Oral Cavity	-	-	-	-	0.7	0.7	9.4	3.3	4.0	11.5	**1.6**	**1.2**	**1.4**
Tonsil	-	-	1.3	0.7	33.4	7.4	49.7	16.0	24.2	18.4	**17.5**	**5.5**	**11.4**
Nasal Cavity	-	0.4	1.0	2.0	5.5	4.7	13.0	14.0	32.3	29.9	**4.4**	**5.4**	**4.9**
Larynx	-	-	1.7	1.0	31.7	5.1	174.4	30.1	185.5	18.4	**38.1**	**6.9**	**22.4**

Projected Population in Britsh Columbia

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
	M	F	M	F	M	F	M	F	M	F	M	F	Total
2003	506,913	479,270	585,735	583,505	617,044	625,070	290,012	308,923	54,975	95,133	**2,054,679**	**2,091,901**	***4,146,580***
2004	500,753	473,548	587,111	584,240	629,956	639,836	296,880	314,795	58,268	99,617	**2,072,968**	**2,112,036**	***4,185,004***
2005	495,622	469,011	590,672	587,222	641,767	652,947	303,750	321,077	61,163	103,443	**2,092,974**	**2,133,700**	***4,226,674***
2006	491,625	465,546	596,619	592,233	650,438	663,333	311,760	328,949	63,942	106,701	**2,114,384**	**2,156,762**	***4,271,146***
2007	489,094	462,718	603,125	599,215	653,766	667,492	324,249	341,764	66,567	109,623	**2,136,801**	**2,180,812**	***4,317,613***
2008	486,956	460,608	609,670	605,000	657,220	672,792	336,488	354,642	68,914	111,757	**2,159,248**	**2,204,799**	***4,364,047***
2009	484,846	458,813	616,399	610,508	662,151	679,317	348,143	367,410	71,237	113,825	**2,182,776**	**2,229,873**	***4,412,649***
2010	483,130	457,027	623,190	616,607	667,214	685,738	360,233	380,850	73,741	115,951	**2,207,508**	**2,256,173**	***4,463,681***
2011	482,022	455,899	630,203	622,816	672,210	692,124	372,244	394,456	76,285	117,910	**2,232,964**	**2,283,205**	***4,516,169***
2012	481,403	455,374	638,943	631,154	675,272	695,945	384,815	408,992	78,514	119,337	**2,258,947**	**2,310,802**	***4,569,749***
2013	481,647	455,594	648,115	639,597	677,559	698,693	397,929	424,491	80,379	120,755	**2,285,629**	**2,339,130**	***4,624,759***
2014	482,541	456,550	657,771	648,485	678,843	699,972	411,933	441,576	81,946	121,651	**2,313,034**	**2,368,234**	***4,681,268***
2015	483,420	457,720	667,188	657,013	679,700	700,546	426,692	459,297	83,451	122,869	**2,340,451**	**2,397,445**	***4,737,896***
2016	484,791	459,009	675,882	664,813	680,374	701,474	441,220	476,716	85,066	124,229	**2,367,333**	**2,426,241**	***4,793,574***
2017	487,132	461,291	682,811	671,454	681,488	702,015	456,040	494,470	86,383	125,585	**2,393,854**	**2,454,815**	***4,848,669***
2018	490,364	464,172	688,096	676,807	682,086	702,383	471,400	512,348	87,803	127,208	**2,419,749**	**2,482,918**	***4,902,667***

Source: PEOPLE29

Projected New Cancer Cases in Britsh Columbia

Cervix

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	M	F	M	F	M	F	M	F	M	F	M	F	Total
2003	-	-	-	41	-	70	-	29	-	11	**-**	**151**	***151***
2004				42		64		33		11	**-**	**150**	***150***
2005				41		63		32		11	**-**	**147**	***147***
2006				40		62		32		11	**-**	**145**	***145***
2007				39		60		32		11	**-**	**142**	***142***
2008				38		59		32		11	**-**	**140**	***140***
2009				37		57		32		11	**-**	**137**	***137***
2010				36		56		32		11	**-**	**135**	***135***
2011				36		54		32		10	**-**	**132**	***132***
2012				35		53		32		10	**-**	**130**	***130***
2013				34		51		33		10	**-**	**128**	***128***
2014				33		50		33		10	**-**	**126**	***126***
2015				33		48		33		9	**-**	**123**	***123***
2016				32		46		33		9	**-**	**120**	***120***
2017				31		45		33		9	**-**	**118**	***118***
2018				30		43		33		9	**-**	**115**	***115***

Projected New Cancer Cases in Britsh Columbia

Vulva

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	M	F	M	F	M	F	M	F	M	F	M	F	Total
2003		0.8		12.7		44.0		23.5		13.8	**-**	**95**	***95***
2004		0.8		12.7		45.0		24.0		14.5	**-**	**97**	***97***
2005		0.8		12.7		45.9		24.4		15.0	**-**	**99**	***99***
2006		0.8		12.9		46.6		25.0		15.5	**-**	**101**	***101***
2007		0.8		13.0		46.9		26.0		15.9	**-**	**103**	***103***
2008		0.8		13.1		47.3		27.0		16.2	**-**	**104**	***104***
2009		0.8		13.2		47.8		28.0		16.5	**-**	**106**	***106***
2010		0.8		13.4		48.2		29.0		16.8	**-**	**108**	***108***
2011		0.7		13.5		48.7		30.0		17.1	**-**	**110**	***110***
2012		0.7		13.7		48.9		31.1		17.3	**-**	**112**	***112***
2013		0.7		13.9		49.1		32.3		17.5	**-**	**114**	***114***
2014		0.8		14.1		49.2		33.6		17.7	**-**	**115**	***115***
2015		0.8		14.3		49.3		35.0		17.8	**-**	**117**	***117***
2016		0.8		14.4		49.3		36.3		18.0	**-**	**119**	***119***
2017		0.8		14.6		49.4		37.6		18.2	**-**	**121**	***121***
2018		0.8		14.7		49.4		39.0		18.5	**-**	**122**	***122***

Projected New Cancer Cases in Britsh Columbia
Vagina

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003		-		1.4		6.1		8.7		4.2	**-**	**20**	***20***
2004		-		1.4		6.3		8.8		4.4	**-**	**21**	***21***
2005		-		1.4		6.4		9.0		4.5	**-**	**21**	***21***
2006		-		1.4		6.5		9.2		4.7	**-**	**22**	***22***
2007		-		1.4		6.5		9.6		4.8	**-**	**22**	***22***
2008		-		1.4		6.6		9.9		4.9	**-**	**23**	***23***
2009		-		1.4		6.7		10.3		5.0	**-**	**23**	***23***
2010		-		1.5		6.7		10.7		5.1	**-**	**24**	***24***
2011		-		1.5		6.8		11.1		5.2	**-**	**24**	***24***
2012		-		1.5		6.8		11.5		5.2	**-**	**25**	***25***
2013		-		1.5		6.8		11.9		5.3	**-**	**26**	***26***
2014		-		1.5		6.9		12.4		5.3	**-**	**26**	***26***
2015		-		1.6		6.9		12.9		5.4	**-**	**27**	***27***
2016		-		1.6		6.9		13.4		5.4	**-**	**27**	***27***
2017		-		1.6		6.9		13.9		5.5	**-**	**28**	***28***
2018		-		1.6		6.9		14.4		5.6	**-**	**28**	***28***

Projected New Cancer Cases in Britsh Columbia
Anus

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	-	1.0	0.4	4.0	1.5	0.8	3.9	1.1	0.9	**7**	**7**	***14***
2004	-	-	1.0	0.4	4.1	1.5	0.9	4.0	1.2	0.9	**7**	**7**	***14***
2005	-	-	1.0	0.4	4.2	1.5	0.9	4.1	1.2	1.0	**7**	**7**	***14***
2006	-	-	1.0	0.4	4.2	1.6	0.9	4.2	1.3	1.0	**7**	**7**	***15***
2007	-	-	1.0	0.4	4.2	1.6	0.9	4.3	1.3	1.0	**8**	**7**	***15***
2008	-	-	1.0	0.4	4.3	1.6	1.0	4.5	1.4	1.0	**8**	**8**	***15***
2009	-	-	1.0	0.4	4.3	1.6	1.0	4.7	1.4	1.0	**8**	**8**	***15***
2010	-	-	1.0	0.4	4.3	1.6	1.0	4.8	1.5	1.1	**8**	**8**	***16***
2011	-	-	1.1	0.4	4.4	1.6	1.1	5.0	1.5	1.1	**8**	**8**	***16***
2012	-	-	1.1	0.4	4.4	1.6	1.1	5.2	1.6	1.1	**8**	**8**	***17***
2013	-	-	1.1	0.4	4.4	1.7	1.1	5.4	1.6	1.1	**8**	**9**	***17***
2014	-	-	1.1	0.4	4.4	1.7	1.2	5.6	1.7	1.1	**8**	**9**	***17***
2015	-	-	1.1	0.4	4.4	1.7	1.2	5.8	1.7	1.1	**8**	**9**	***18***
2016	-	-	1.1	0.5	4.4	1.7	1.3	6.0	1.7	1.1	**9**	**9**	***18***
2017	-	-	1.1	0.5	4.4	1.7	1.3	6.3	1.7	1.2	**9**	**10**	***18***
2018	-	-	1.2	0.5	4.4	1.7	1.4	6.5	1.8	1.2	**9**	**10**	***18***

Projected New Cancer Cases in Britsh Columbia
Penis

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-		2.8		7.4		17.1		2.7		**30**	**-**	***30***
2004	-		2.8		7.5		17.5		2.8		**31**	**-**	***31***
2005	-		2.8		7.7		17.9		3.0		**31**	**-**	***31***
2006	-		2.8		7.8		18.4		3.1		**32**	**-**	***32***
2007	-		2.8		7.8		19.2		3.2		**33**	**-**	***33***
2008	-		2.9		7.8		19.9		3.3		**34**	**-**	***34***
2009	-		2.9		7.9		20.6		3.4		**35**	**-**	***35***
2010	-		2.9		8.0		21.3		3.6		**36**	**-**	***36***
2011	-		3.0		8.0		22.0		3.7		**37**	**-**	***37***
2012	-		3.0		8.1		22.7		3.8		**38**	**-**	***38***
2013	-		3.1		8.1		23.5		3.9		**39**	**-**	***39***
2014	-		3.1		8.1		24.3		4.0		**40**	**-**	***40***
2015	-		3.1		8.1		25.2		4.0		**41**	**-**	***41***
2016	-		3.2		8.1		26.1		4.1		**41**	**-**	***41***
2017	-		3.2		8.1		26.9		4.2		**42**	**-**	***42***
2018	-		3.2		8.1		27.9		4.2		**43**	**-**	***43***

Projected New Cancer Cases in Britsh Columbia
Conjunctiva

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	-	-	-	-	0.2	0.4	-	0.7	-	**1**	**0**	***1***
2004	-	-	-	-	-	0.2	0.4	-	0.7	-	**1**	**0**	***1***
2005	-	-	-	-	-	0.2	0.4	-	0.7	-	**1**	**0**	***1***
2006	-	-	-	-	-	0.2	0.4	-	0.8	-	**1**	**0**	***1***
2007	-	-	-	-	-	0.2	0.5	-	0.8	-	**1**	**0**	***1***
2008	-	-	-	-	-	0.2	0.5	-	0.8	-	**1**	**0**	***2***
2009	-	-	-	-	-	0.2	0.5	-	0.9	-	**1**	**0**	***2***
2010	-	-	-	-	-	0.2	0.5	-	0.9	-	**1**	**0**	***2***
2011	-	-	-	-	-	0.2	0.5	-	0.9	-	**1**	**0**	***2***
2012	-	-	-	-	-	0.2	0.6	-	0.9	-	**2**	**0**	***2***
2013	-	-	-	-	-	0.2	0.6	-	1.0	-	**2**	**0**	***2***
2014	-	-	-	-	-	0.2	0.6	-	1.0	-	**2**	**0**	***2***
2015	-	-	-	-	-	0.2	0.6	-	1.0	-	**2**	**0**	***2***
2016	-	-	-	-	-	0.2	0.6	-	1.0	-	**2**	**0**	***2***
2017	-	-	-	-	-	0.2	0.7	-	1.0	-	**2**	**0**	***2***
2018	-	-	-	-	-	0.2	0.7	-	1.1	-	**2**	**0**	***2***

Projected New Cancer Cases in Britsh Columbia
Oral Cavity

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	-	-	-	0.4	0.4	2.7	1.0	0.2	1.1	**3**	**3**	***6***
2004	-	-	-	-	0.4	0.4	2.8	1.1	0.2	1.1	**3**	**3**	***6***
2005	-	-	-	-	0.4	0.4	2.8	1.1	0.2	1.2	**4**	**3**	***6***
2006	-	-	-	-	0.4	0.4	2.9	1.1	0.3	1.2	**4**	**3**	***6***
2007	-	-	-	-	0.4	0.5	3.0	1.1	0.3	1.3	**4**	**3**	***7***
2008	-	-	-	-	0.4	0.5	3.2	1.2	0.3	1.3	**4**	**3**	***7***
2009	-	-	-	-	0.5	0.5	3.3	1.2	0.3	1.3	**4**	**3**	***7***
2010	-	-	-	-	0.5	0.5	3.4	1.3	0.3	1.3	**4**	**3**	***7***
2011	-	-	-	-	0.5	0.5	3.5	1.3	0.3	1.4	**4**	**3**	***7***
2012	-	-	-	-	0.5	0.5	3.6	1.4	0.3	1.4	**4**	**3**	***8***
2013	-	-	-	-	0.5	0.5	3.7	1.4	0.3	1.4	**5**	**3**	***8***
2014	-	-	-	-	0.5	0.5	3.9	1.5	0.3	1.4	**5**	**3**	***8***
2015	-	-	-	-	0.5	0.5	4.0	1.5	0.3	1.4	**5**	**3**	***8***
2016	-	-	-	-	0.5	0.5	4.1	1.6	0.3	1.4	**5**	**3**	***8***
2017	-	-	-	-	0.5	0.5	4.3	1.7	0.3	1.4	**5**	**4**	***9***
2018	-	-	-	-	0.5	0.5	4.4	1.7	0.4	1.5	**5**	**4**	***9***

Projected New Cancer Cases in Britsh Columbia
Tonsil

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	-	0.8	0.4	20.6	4.6	14.4	5.0	1.3	1.8	**37**	**12**	***49***
2004	-	-	0.8	0.4	21.0	4.8	14.8	5.0	1.4	1.8	**38**	**12**	***50***
2005	-	-	0.8	0.4	21.4	4.9	15.1	5.1	1.5	1.9	**39**	**12**	***51***
2006	-	-	0.8	0.4	21.7	4.9	15.5	5.3	1.5	2.0	**40**	**13**	***52***
2007	-	-	0.8	0.4	21.8	5.0	16.1	5.5	1.6	2.0	**40**	**13**	***53***
2008	-	-	0.8	0.4	22.0	5.0	16.7	5.7	1.7	2.1	**41**	**13**	***54***
2009	-	-	0.8	0.4	22.1	5.1	17.3	5.9	1.7	2.1	**42**	**13**	***55***
2010	-	-	0.8	0.4	22.3	5.1	17.9	6.1	1.8	2.1	**43**	**14**	***57***
2011	-	-	0.8	0.4	22.5	5.1	18.5	6.3	1.8	2.2	**44**	**14**	***58***
2012	-	-	0.9	0.4	22.6	5.2	19.1	6.6	1.9	2.2	**44**	**14**	***59***
2013	-	-	0.9	0.4	22.6	5.2	19.8	6.8	1.9	2.2	**45**	**15**	***60***
2014	-	-	0.9	0.4	22.7	5.2	20.5	7.1	2.0	2.2	**46**	**15**	***61***
2015	-	-	0.9	0.4	22.7	5.2	21.2	7.4	2.0	2.3	**47**	**15**	***62***
2016	-	-	0.9	0.5	22.7	5.2	21.9	7.6	2.1	2.3	**48**	**16**	***63***
2017	-	-	0.9	0.5	22.8	5.2	22.7	7.9	2.1	2.3	**48**	**16**	***64***
2018	-	-	0.9	0.5	22.8	5.2	23.4	8.2	2.1	2.3	**49**	**16**	***66***

Projected New Cancer Cases in Britsh Columbia

Nasal Cavity

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	0.2	0.6	1.2	3.4	3.0	3.8	4.3	1.8	2.8	**9**	**12**	***21***
2004	-	0.2	0.6	1.2	3.4	3.0	3.9	4.4	1.9	3.0	**10**	**12**	***22***
2005	-	0.2	0.6	1.2	3.5	3.1	3.9	4.5	2.0	3.1	**10**	**12**	***22***
2006	-	0.2	0.6	1.2	3.5	3.1	4.0	4.6	2.1	3.2	**10**	**12**	***23***
2007	-	0.2	0.6	1.2	3.6	3.2	4.2	4.8	2.1	3.3	**11**	**13**	***23***
2008	-	0.2	0.6	1.2	3.6	3.2	4.4	5.0	2.2	3.3	**11**	**13**	***24***
2009	-	0.2	0.6	1.2	3.6	3.2	4.5	5.2	2.3	3.4	**11**	**13**	***24***
2010	-	0.2	0.6	1.3	3.6	3.2	4.7	5.3	2.4	3.5	**11**	**14**	***25***
2011	-	0.2	0.6	1.3	3.7	3.3	4.8	5.5	2.5	3.5	**12**	**14**	***25***
2012	-	0.2	0.6	1.3	3.7	3.3	5.0	5.7	2.5	3.6	**12**	**14**	***26***
2013	-	0.2	0.7	1.3	3.7	3.3	5.2	6.0	2.6	3.6	**12**	**14**	***26***
2014	-	0.2	0.7	1.3	3.7	3.3	5.3	6.2	2.6	3.6	**12**	**15**	***27***
2015	-	0.2	0.7	1.3	3.7	3.3	5.5	6.4	2.7	3.7	**13**	**15**	***28***
2016	-	0.2	0.7	1.4	3.7	3.3	5.7	6.7	2.7	3.7	**13**	**15**	***28***
2017	-	0.2	0.7	1.4	3.7	3.3	5.9	6.9	2.8	3.8	**13**	**16**	***29***
2018	-	0.2	0.7	1.4	3.7	3.3	6.1	7.2	2.8	3.8	**13**	**16**	***29***

Projected New Cancer Cases in Britsh Columbia

Larynx

	0 - 19		20 - 39		40 - 59		60 - 79		80+		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-	-	1.0	0.6	19.6	3.2	50.6	9.3	10.2	1.8	**81**	**15**	***96***
2004	-	-	1.0	0.6	20.0	3.2	51.8	9.5	10.8	1.8	**84**	**15**	***99***
2005	-	-	1.0	0.6	20.3	3.3	53.0	9.6	11.3	1.9	**86**	**15**	***101***
2006	-	-	1.0	0.6	20.6	3.4	54.4	9.9	11.9	2.0	**88**	**16**	***104***
2007	-	-	1.0	0.6	20.7	3.4	56.5	10.3	12.3	2.0	**91**	**16**	***107***
2008	-	-	1.0	0.6	20.8	3.4	58.7	10.7	12.8	2.1	**93**	**17**	***110***
2009	-	-	1.0	0.6	21.0	3.4	60.7	11.0	13.2	2.1	**96**	**17**	***113***
2010	-	-	1.0	0.6	21.2	3.5	62.8	11.4	13.7	2.1	**99**	**18**	***116***
2011	-	-	1.1	0.6	21.3	3.5	64.9	11.9	14.1	2.2	**101**	**18**	***120***
2012	-	-	1.1	0.6	21.4	3.5	67.1	12.3	14.6	2.2	**104**	**19**	***123***
2013	-	-	1.1	0.7	21.5	3.5	69.4	12.8	14.9	2.2	**107**	**19**	***126***
2014	-	-	1.1	0.7	21.5	3.5	71.8	13.3	15.2	2.2	**110**	**20**	***129***
2015	-	-	1.1	0.7	21.6	3.6	74.4	13.8	15.5	2.3	**113**	**20**	***133***
2016	-	-	1.1	0.7	21.6	3.6	76.9	14.3	15.8	2.3	**115**	**21**	***136***
2017	-	-	1.1	0.7	21.6	3.6	79.5	14.9	16.0	2.3	**118**	**21**	***140***
2018	-	-	1.2	0.7	21.6	3.6	82.2	15.4	16.3	2.3	**121**	**22**	***143***

Projected New Cancer Cases in Britsh Columbia

HPV Related Cancers

	Cervix		Vulva		Vagina		Anus		Penis		Conjunctiva		Oral		Tonsil		Nasal		Larynx				
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003		151		95		20	7	7	30		1	0	3	3	37	12	9	12	81	15	**169**	**314**	***483***
2004		150		97		21	7	7	31		1	0	3	3	38	12	10	12	84	15	**174**	**316**	***490***
2005		147		99		21	7	7	31		1	0	4	3	39	12	10	12	86	15	**178**	**317**	***495***
2006		145		101		22	7	7	32		1	0	4	3	40	13	10	12	88	16	**182**	**318**	***500***
2007		142		103		22	8	7	33		1	0	4	3	40	13	11	13	91	16	**187**	**319**	***506***
2008		140		104		23	8	8	34		1	0	4	3	41	13	11	13	93	17	**192**	**321**	***513***
2009		137		106		23	8	8	35		1	0	4	3	42	13	11	13	96	17	**197**	**321**	***518***
2010		135		108		24	8	8	36		1	0	4	3	43	14	11	14	99	18	**202**	**323**	***525***
2011		132		110		24	8	8	37		1	0	4	3	44	14	12	14	101	18	**207**	**324**	***531***
2012		130		112		25	8	8	38		2	0	4	3	44	14	12	14	104	19	**212**	**326**	***538***
2013		128		114		26	8	9	39		2	0	5	3	45	15	12	14	107	19	**217**	**327**	***545***
2014		126		115		26	8	9	40		2	0	5	3	46	15	12	15	110	20	**222**	**329**	***551***
2015		123		117		27	8	9	41		2	0	5	3	47	15	13	15	113	20	**227**	**330**	***557***
2016		120		119		27	9	9	41		2	0	5	3	48	16	13	15	115	21	**233**	**331**	***563***
2017		118		121		28	9	10	42		2	0	5	4	48	16	13	16	118	21	**238**	**333**	***570***
2018		115		122		28	9	10	43		2	0	5	4	49	16	13	16	121	22	**243**	**334**	***577***

Projected New Cancer Cases in Britsh Columbia

Due to HPV Infection

	Cervix		Vulva		Vagina		Anus		Penis		Conjunctiva		Oral		Tonsil		Nasal		Larynx				
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003		151		52		11	6	6	13		1	0	1	1	19	6	2	3	20	4	**61**	**233**	***294***
2004		150		53		11	6	6	13		1	0	1	1	19	6	2	3	21	4	**63**	**234**	***297***
2005		147		54		12	6	6	13		1	0	1	1	20	6	2	3	21	4	**64**	**233**	***297***
2006		145		55		12	7	6	13		1	0	1	1	20	6	2	3	22	4	**66**	**232**	***298***
2007		142		56		12	7	6	14		1	0	1	1	21	7	2	3	23	4	**68**	**231**	***299***
2008		140		57		12	7	7	14		1	0	1	1	21	7	2	3	23	4	**69**	**231**	***300***
2009		137		58		13	7	7	15		1	0	1	1	21	7	2	3	24	4	**71**	**230**	***301***
2010		135		59		13	7	7	15		1	0	1	1	22	7	2	3	25	4	**73**	**230**	***302***
2011		132		61		13	7	7	15		1	0	1	1	22	7	3	3	25	5	**74**	**228**	***303***
2012		130		62		14	7	7	16		1	0	1	1	23	7	3	3	26	5	**76**	**228**	***304***
2013		128		62		14	7	8	16		1	0	1	1	23	7	3	3	27	5	**78**	**228**	***306***
2014		126		63		14	7	8	17		1	0	1	1	23	8	3	3	27	5	**79**	**228**	***307***
2015		123		64		14	7	8	17		1	0	1	1	24	8	3	3	28	5	**81**	**227**	***308***
2016		120		65		15	8	8	17		1	0	1	1	24	8	3	3	29	5	**83**	**226**	***309***
2017		118		66		15	8	8	18		1	0	1	1	25	8	3	3	30	5	**85**	**226**	***310***
2018		115		67		15	8	9	18		1	0	1	1	25	8	3	3	30	5	**86**	**224**	***311***

Projected New Cancer Cases in Britsh Columbia

Due to HPV 16/18 Infection

	Cervix		Vulva		Vagina		Anus		Penis		Conjunctiva		Oral		Tonsil		Nasal		Larynx		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003		100		52		8	5	5	8		1	0	1	1	16	5	2	3	20	4	**52**	**176**	***229***
2004		99		53		8	5	5	8		1	0	1	1	16	5	2	3	21	4	**54**	**177**	***231***
2005		97		54		8	5	5	8		1	0	1	1	17	5	2	3	21	4	**55**	**177**	***232***
2006		96		55		8	5	5	8		1	0	1	1	17	5	2	3	22	4	**56**	**177**	***234***
2007		94		56		9	5	5	9		1	0	1	1	17	6	2	3	23	4	**58**	**177**	***235***
2008		92		57		9	5	5	9		1	0	1	1	18	6	2	3	23	4	**59**	**177**	***237***
2009		90		58		9	5	5	9		1	0	1	1	18	6	2	3	24	4	**61**	**177**	***238***
2010		89		59		9	6	6	9		1	0	1	1	18	6	2	3	25	4	**62**	**177**	***240***
2011		87		61		9	6	6	10		1	0	1	1	19	6	3	3	25	5	**64**	**177**	***241***
2012		86		62		10	6	6	10		1	0	1	1	19	6	3	3	26	5	**65**	**178**	***243***
2013		84		62		10	6	6	10		1	0	1	1	19	6	3	3	27	5	**67**	**178**	***244***
2014		83		63		10	6	6	10		1	0	1	1	20	6	3	3	27	5	**68**	**178**	***246***
2015		81		64		10	6	6	11		1	0	1	1	20	7	3	3	28	5	**70**	**178**	***247***
2016		79		65		10	6	7	11		1	0	1	1	20	7	3	3	29	5	**71**	**178**	***249***
2017		78		66		11	6	7	11		1	0	1	1	21	7	3	3	30	5	**72**	**178**	***251***
2018		76		67		11	6	7	12		1	0	1	1	21	7	3	3	30	5	**74**	**178**	***252***

Projected New Cancer Cases in Britsh Columbia

Due to HPV 6/11 Infection

	Cervix		Vulva		Vagina		Anus		Penis		Conjunctiva		Oral		Tonsil		Nasal		Larynx		TOTAL		
Year	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**Total**
2003	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2004	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2005	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2006	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2007	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2008	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2009	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2010	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2011	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2012	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2013	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2014	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***3***
2015	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***4***
2016	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***4***
2017	-		-		1		-	-	1		-	-	-	-	1	0	-	-	-	-	**2**	**1**	***4***
2018	-		-		1		-	-	2		-	-	-	-	1	0	-	-	-	-	**2**	**2**	***4***

Non-Malignant Disease HPV-Related Disease
Estimated Annual Incidence in British Columbia

	Genital Warts		RPP - Children		RPP - Adults		Sino-Nasal	
	M	F	M	F	M	F	M	F
2003	3,415	3,570	3	3	29	30	19	6
2004	3,445	3,608	3	3	29	30	19	6
2005	3,478	3,647	3	3	30	31	19	6
2006	3,517	3,685	3	3	30	31	19	6
2007	3,562	3,723	3	3	31	32	19	6
2008	3,610	3,756	3	3	31	32	20	7
2009	3,660	3,788	3	3	32	33	20	7
2010	3,711	3,823	3	3	32	33	20	7
2011	3,762	3,858	3	3	33	34	20	7
2012	3,809	3,889	3	3	33	34	21	7
2013	3,854	3,918	3	3	33	35	21	7
2014	3,899	3,944	3	3	34	35	21	7
2015	3,943	3,969	3	3	34	36	21	7
2016	3,983	3,992	3	3	35	36	22	7
2017	4,020	4,012	3	3	35	37	22	7
2018	4,050	4,028	3	3	36	37	22	7

Non-Malignant Disease HPV-Related Disease
Due to HPV 6/11 Infection

	Genital Warts		RPP - Children		RPP - Adults		Sino-Nasal	
	M	F	M	F	M	F	M	F
2003	3,073	3,213	3	3	29	30	19	6
2004	3,100	3,248	3	3	29	30	19	6
2005	3,130	3,282	3	3	30	31	19	6
2006	3,165	3,317	3	3	30	31	19	6
2007	3,206	3,351	3	3	31	32	19	6
2008	3,249	3,380	3	3	31	32	20	7
2009	3,294	3,409	3	3	32	33	20	7
2010	3,340	3,441	3	3	32	33	20	7
2011	3,385	3,472	3	3	33	34	20	7
2012	3,428	3,500	3	3	33	34	21	7
2013	3,468	3,526	3	3	33	35	21	7
2014	3,509	3,550	3	3	34	35	21	7
2015	3,548	3,572	3	3	34	36	21	7
2016	3,585	3,593	3	3	35	36	22	7
2017	3,618	3,611	3	3	35	37	22	7
2018	3,645	3,625	3	3	36	37	22	7

Appendix B: Estimating the Cost of HPV Infection in British Columbia

In estimating the cost of HPV infection in British Columbia, we used the following approach and made the following assumptions:

- According to the 2004 B.C. Cancer Agency Cervical Cancer Screening Program 2004 Annual Report, 577,718 conventional cytology smears were provided to women in B.C. in 2003. Additional information from that report is indicated on the following table.

Cervical Cancer Screening in BC Based on 2004 Annual Report	
Cervical Cancer (2003)	
Conventional Cytology	
# of Smears	577,718
# of Patients	538,021
Negative Result	473,323
Reactive Changes	16,989
Mild Atypia	
# of Patients	24,858
Recommend Colposcopy	2,407
Level of Compliance	73%
Estimated # of Colposcopies	1,757
Moderate or Higher Atypia	
# of Patients	6,197
Recommend Colposcopy and/or Endocervical Curettage	5,422
Other Investigation	775
Level of Compliance	76%
Estimated # of Colposcopies	4,121
Estimated # of Colposcopy/Biopsy	589
Total Colposcopies in BC (2003)	12,732
Site = Cervix	11,841

- Based on this information, we assumed that 11,841 colposcopies were provided with the cervix as the site and that 589 colposcopy plus biopsies were provided (based on the 775 recommended 'other investigations' for moderate or higher atypia, with a 76% compliance rate).

- The estimated 147 cervical cancers in 2005 (see the table in Appendix A) would be equally divided between local, regional and distant invasive cancers.

- Estimated costs for a conventional cytology were taken from the study by Kim et al.[651] which provided costs for each of these procedures in four

[651] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. *Journal of the National Cancer Institute.* 2005; 97(12): 888-95.

countries in Europe (the UK, Netherlands, France and Italy). We used the average cost for these four countries for an estimate of $40.00. This coincides with an estimate based on a $12.50 cytology laboratory cost and a $27.50 general practitioner visit cost (current estimates for British Columbia).

- Estimated costs for a colposcopy, a colposcopy plus biopsy, and for local, regional and distant invasive cancers were taken from the study by Kim et al.[652] which provided costs for each of these procedures in four countries in Europe (the UK, Netherlands, France and Italy). We used the average cost for these four countries.

- The costs in the Kim et al.[653] study were provided in 2004 US dollars. We converted this to Canadian dollars (multiplying by 1.19) and then updated to 2005 dollars. The update to current dollars is based on increases in the health care component of the Consumer Price Index. To increase dollars from a given year to 2005, the following increases were used:

    - 1996 to 2005 – 23.06%
    - 1997 to 2005 – 21.47%
    - 1998 to 2005 – 18.11%
    - 1999 to 2005 – 15.53%
    - 2000 to 2005 – 12.38%
    - 2001 to 2005 – 8.96%
    - 2002 to 2005 – 7.73%
    - 2003 to 2005 – 3.66%
    - 2004 to 2005 – 1.90%

- For the costs associated with anogenital cancers we used studies by Goldie et al.[654] and Uyl-De Groot et al.[655] to estimate the cost of primary treatment of cancer of the vulva and cancer of the anus, respectively. The costs for cancer of the anus, provided in euros, were converted to Canadian dollars (multiplying by 1.45). In addition to the primary treatment costs, we added an additional 45% to take into account work-up, treatment of recurrent tumours, and long-term follow-up, based on other cancer studies by van Agthoven et al.[656] and Nijdam et al.[657] We were unable to find published cost

[652] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. *Journal of the National Cancer Institute.* 2005; 97(12): 888-95.
[653] Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and Italy. *Journal of the National Cancer Institute.* 2005; 97(12): 888-95.
[654] Goldie SJ, Kuntz KM, Weinstein MC et al. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *American Journal of Medicine.* 2000; 108(8): 634-41.
[655] Uyl-De Groot CA, Hartog JG, Derksen JG et al. Cost-effectiveness and quality of life of granulocyte-colony stimulating factor (filgrastim) after radical vulvectomy and bilateral inguino-femoral lymphadenectomy: results of a randomized clinical trial. *European Journal of Obstetrics & Gynecology & Reproductive Biology.* 2004; 114(1): 77-82.
[656] van Agthoven M, van Ineveld BM, de Boer MF et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. *European Journal of Cancer.* 2001; 37(17): 2204-11.

information on cancers of the vagina and penis, and thus estimated these as an average of vulvar and anal cancer costs.

- For the costs associated with cancers of the head and neck, we used the study by Nijdam et al.[658] to estimate the cost of treating cancer of the tonsils. This included costs associated with the work-up, treatment, relapse and 5-year follow-up. The study by van Agthoven et al.[659] was used for cancer of the larynx, sinonasal cancers and oral cancers. This study also included costs associated with the work-up, treatment, relapse and 10 year follow-up.

- For the cost of genital warts we used the study by Insigna et al.[660] The average cost provided in this paper was almost identical to a cost calculated using the midpoint of the low and high range of costs presented in other studies (see section on *The Cost of Treating HPV-related Disease*).

- The costs associated with recurrent respiratory papillomatosis are based on a study by Bishai et al.[661] The costs associated with the disease in children is higher than that in adults. Based on results in the study by Long and Sani,[662] we assumed that the costs in adults would be 70% of the costs in children (see section on *The Cost of Treating HPV-related Disease*).

A synthesis of these assumptions on costs, together with estimates of the clinical impact of HPV infection in B.C., is indicated on the following table.

[657] Nijdam W, Levendag P, Noever I et al. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(2): 488-94.
[658] Nijdam W, Levendag P, Noever I et al. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. *International Journal of Radiation Oncology, Biology, Physics.* 2004; 59(2): 488-94.
[659] van Agthoven M, van Ineveld BM, de Boer MF et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. *European Journal of Cancer.* 2001; 37(17): 2204-11.
[660] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clinical Infectious Diseases.* 2003; 36(11): 1397-403.
[661] Bishai D, Kashima H, Shah K. The cost of juvenile-onset recurrent respiratory papillomatosis. *Archives of Otolaryngology -- Head and Neck Surgery.* 2000; 126(8): 935-9.
[662] Long Y, Sani A. Recurrent Respiratory Papillomatosis. Asian Journal of Surgery. 2003; 26(2): 112-116.

Estimated Cost of HPV Infection in British Columbia in 2005

	Estimated New Cases in 2005	Estimated Cost	Currency	Year	Convert to Can$	Update to 2005$	Est. Cost in BC	Notes
Cervical Cancer								
Conventional Cytology	577,718	33	US$	2004	$ 39	$ 40	$ 23,118,039	Based on average for UK, Netherlands, France and Italy
Colposcopy	11,841	114	US$	2004	$ 136	$ 139	$ 1,641,657	Based on average for UK, Netherlands, and Italy
Colposcopy and Biopsy	589	201	US$	2004	$ 239	$ 244	$ 143,560	Based on average for UK, Netherlands, and Italy
Local Invasive Cervical Cancer	49	9,662	US$	2004	$ 11,498	$ 11,716	$ 574,096	Based on average for UK, Netherlands, and France
Regional Invasive Cervical Cancer	49	19,585	US$	2004	$ 23,306	$ 23,749	$ 1,163,699	Based on average for UK, Netherlands, and France
Distant Invasive Cervical Cancer	49	29,670	US$	2004	$ 35,308	$ 35,979	$ 1,762,949	Based on average for UK, Netherlands, and France
Anogenital Cancers								
Vulva	54	20,312	€	2002	$ 29,452	$ 31,139	$ 1,681,528	Add 45% for work-up, treatment of recurrent tumours, and long-term follow-up
Vagina	12					$ 37,787	$ 453,443	Use average estimate for vulva and anus
Penis	13					$ 37,787	$ 491,230	Use average estimate for vulva and anus
Anus	12	30,740	US$	1997	$ 36,581	$ 44,434	$ 533,213	Add 45% for work-up, treatment of recurrent tumours, and long-term follow-up
Cancers of the Head and Neck								
Tonsils	26	16,522	€	2001	$ 23,957	$ 26,103	$ 678,689	Work-up, treatment, relapse and 5 year follow-up
Larynx	24	26,851	€	1996	$ 38,934	$ 47,912	$ 1,149,891	Work-up, treatment, relapse and 10 year follow-up
Sinonasal	5	35,642	€	1996	$ 51,681	$ 63,599	$ 317,993	Work-up, treatment, relapse and 10 year follow-up
Oral	2	35,541	€	1996	$ 51,534	$ 63,418	$ 126,837	Work-up, treatment, relapse and 10 year follow-up
Non-Malignant Diseases								
Genital Warts	6,286	436	US$	2002	$ 519	$ 549	$ 3,448,308	Complete episode of care
Recurrent Respiratory Papillomatosis								
Children	5	99,500	US$	1997	$ 118,405	$ 143,827	$ 719,133	Cost per new case over 4.2 years
Adults	45					$ 100,679	$ 4,530,536	70% of juvenile costs
Total Estimated Cost in 2005							**$ 42,534,800**	

A second approach to estimating the cost of *cervical* HPV infection in British Columbia involves modifying the assumptions associated with the treatment of Pap smear false-positive results and the management of cervical precancers. In the above approach, our focus was on colposcopy and biopsy tests, which does not fully take into account the array of tests and procedures used in addressing, for example, the treatment of precancers (see the section on *The Cost of Treating HPV-related Disease*).

Insinga and colleagues[663] found the following breakdown of total HPV-related cervical disease program costs:

- Routine cervical screening - 64%
- Dealing with false-positive results - 9%
- Management of cervical precancers - 17%
- Treating invasive cervical cancers - 10%

Our B.C. estimate for routine cervical screening is $23.1 million, and for treating invasive cervical cancers, $3.5 million. To achieve a relative distribution similar to that of Insinga and colleagues, we estimated that the cost of dealing with false-positive results would be $3.3 million and the costs of management of cervical precancers would be $6.1.

[663] Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus--related disease. *American Journal of Obstetrics & Gynecology.* 2004; 191(1): 114-20.

Total estimated costs in 2005 of HPV-related cervical disease program costs would be as follows:

Routine cervical screening	- $23.1 million (64.3%)
Dealing with false-positive results	- $3.5 million (9.0%)
Management of cervical precancers	- $6.1 million (17.0%)
Treating invasive cervical cancers	- $3.5 million (9.7%)

It is this approach that we have used in the section of the paper titled *The Cost of Treating HPV-related Diseases in British Columbia.* The figures for false-positive results and precancer management are inserted on their own, rather than being generated from the number of cases.

The Cervical Cancer Screening Program identified 6,197 patients in British Columbia through with moderate or higher atypia in 2003. We have assumed that these patients generate all of the treatment costs for precancer and thus generate an average cost of $984.34 per case ($6.1 million divided by 6,197 cases).

The 2004 annual report of the Cervical Cancer Screening Program in British Columbia indicated that 9.7% of females with mild atypia are referred for a colposcopy. We have used a cost of $139 per colposcopy to estimate the average follow-up cost associated with identifying mild atypia as $13.48 ($139 * 0.097).

The overall results are shown on the following table. The estimated total cost of HPV infection in B.C. for 2005 is just over $50 million.

Estimated Cost of HPV Infection in British Columbia
in 2005

	Estimated New Cases in 2005	Estimated Cost	Currency	Year	Convert to Can$	Update to 2005$	Est. Cost in BC	Notes
Cervical Cancer								
Conventional Cytology	577,718	33	US$	2004	$ 39	$ 40	$ 23,118,039	Based on average for UK, Netherlands, France and Italy
False Positives							$ 3,250,000	9.0% of total program costs
Cervical Precancers							$ 6,100,000	17.0% of total program costs
Local Invasive Cervical Cancer	49	9,662	US$	2004	$ 11,498	$ 11,716	$ 574,096	Based on average for UK, Netherlands, and France
Regional Invasive Cervical Cancer	49	19,585	US$	2004	$ 23,306	$ 23,749	$ 1,163,699	Based on average for UK, Netherlands, and France
Distant Invasive Cervical Cancer	49	29,670	US$	2004	$ 35,308	$ 35,979	$ 1,762,949	Based on average for UK, Netherlands, and France
Anogenital Cancers								
Vulva	54	20,312	€	2002	$ 29,452	$ 31,139	$ 1,681,528	Add 45% for work-up, treatment of recurrent tumours, and long-term follow-up
Vagina	12					$ 37,787	$ 453,443	Use average estimate for vulva and anus
Penis	13					$ 37,787	$ 491,230	Use average estimate for vulva and anus
Anus	12	30,740	US$	1997	$ 36,581	$ 44,434	$ 533,213	Add 45% for work-up, treatment of recurrent tumours, and long-term follow-up
Cancers of the Head and Neck								
Tonsils	26	16,522	€	2001	$ 23,957	$ 26,103	$ 678,689	Work-up, treatment, relapse and 5 year follow-up
Larynx	24	26,851	€	1996	$ 38,934	$ 47,912	$ 1,149,891	Work-up, treatment, relapse and 10 year follow-up
Sinonasal	5	35,642	€	1996	$ 51,681	$ 63,599	$ 317,993	Work-up, treatment, relapse and 10 year follow-up
Oral	2	35,541	€	1996	$ 51,534	$ 63,418	$ 126,837	Work-up, treatment, relapse and 10 year follow-up
Non-Malignant Diseases								
Genital Warts	6,286	436	US$	2002	$ 519	$ 549	$ 3,448,308	Complete episode of care
Recurrent Respiratory Papillomatosis								
Children	5	99,500	US$	1997	$ 118,405	$ 143,827	$ 719,133	Cost per new case over 4.2 years
Adults	45					$ 100,679	$ 4,530,536	70% of juvenile costs
Total Estimated Cost in 2005							**$ 50,099,584**	