MEDICINE

A VACCINE TO ERADICATE CANCER: HIGH HOPES FOR A VACCINE AGAINST HUMAN PAPILLOMAVIRUS

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Cancer — a word we hear and speak too frequently. News outlets run stories about the cancer-fighting properties of wine, coffee and blueberries; we are warned to stay indoors to prevent exposure to damaging solar radiation; and every year we learn of more people whose doctors have pronounced one of the most feared diagnoses. But now, for at least one type of cancer, we have a previously undreamt-of reprieve: a vaccine. Research led by Dr. Diane Harper at Dartmouth-Hitchcock Medical Center has been instrumental in developing a vaccine that may prevent cancer caused by the human papillomavirus (HPV). The vaccine is currently in Phase III testing, the final phase assessing the risk and effectiveness of the drug (1), and there is hope that one version of the vaccine will be available in the US in 2006 and that another will reach the market in early 2007.

Diane Harper

Image courtesy of Mark Washburn

Doctors have speculated about the causes of cervical cancer for more than a century. As early as 1850 an Italian doctor noticed that nuns never developed cervical cancer and hypothesized that sexual activity played a role in the cancer's development. However, no more specific causes were found at that time (2). In 1975, two scientists—one German and one Canadian–simultaneously published papers noting the similarities between wart and cervical cancer specimens (2). The first epidemiological study of HPV determined the relative risk for developing cancer in individuals with and without HPV. Relative risk measures "the ratio of the incidence rate of a disease among individuals exposed to a specific risk factor to the incidence rate among unexposed individuals" (3). For smokers, the relative risk of developing lung cancer is 1.3:1 (2). For women with HPV infections, the relative risk of developing cervical cancer is 400:1 (2).

Over 100 types of HPV are known to exist, but many cannot cause cancer (4). Fifteen types of HPV account for almost all cases of cervical cancer, while others may cause genital warts (5). HPV 16 and HPV 18 infections are present in the majority of cases of cervical cancer (6). HPV 31, HPV 33, and HPV 45 are responsible for another 20% of cases. Ten more types allow researchers to account for almost all of the cases of cervical cancer (2). However, HPV is not responsible only for cancer of the cervix. Anal, vulvar, vaginal, penile, tonsillar, sinus, oro-pharyngeal (head and neck), esophageal, and oral/mouth cancers can also be caused by the oncogenic HPV types (2). Many occurrences of skin cancer that are not melanoma are also caused by HPV (2). Of all cases of cancer worldwide, HPV is responsible for 5% (2).

HPV is a virus of 8,000 base pairs, with a mutation in the base pairs occurring approximately every 10,000 years (2). There are many types of the virus, but all are spread through skin-to-skin contact (2). Due to this simple method of transmission, it is even possible for a person to transmit an infection from one part of his or her body to another (2). The virus lives in the outermost 400 nanometers of skin, never entering the body. This infection

The Dartmouth Hitchcock Medical Center. Image courtesy of Mark Washburn.

strategy reduces the immune system's ability to detect and destroy the virus (2). While many characterize HPV as a sexually transmitted infection (STI), it is different from other STIs in a number of ways. It is the only STI that lives in the skin and is transmitted through skin contact, rather than through body fluids (2). Also, as discussed above, HPV infects areas and causes cancer outside of the genital region, also distinguishing it from other infections characterized as being sexually transmitted. HPV is extraordinarily common, and the types that can cause cancer or genital warts currently infect about 20 million people in the US (7). However, even if a person were to contract one of the oncogenic types of HPV, she still may not develop cervical cancer (2), through chance or a natural immune response from her body (8). Yet over a lifetime, 70% of women who are sexually active will have developed at least one HPV infection (9). Cases of HPV can clear up without treatment, but it is the persistent HPV infections that are a cause for concern, since those cases may lead to cancer (2). While the data are approximate, it has been estimated that, worldwide, there are over half a million new cases of cervical cancer each year, resulting in 230,000 deaths, and that most of these deaths occur in the developing world (2, 6). Deaths due to cervical cancer in the U.S. and Europe number about 35,000 per year (9).

The types of HPV that cause cancer have understandably been the focus of the bulk of HPV research. Dr. Diane Harper, who is associated with Dartmouth Medical School, the Norris Cotton Cancer Center, and the Dartmouth-Hitchcock Medical Center, is the director of several clinical trials that have been run in the U.S., Brazil, Canada, and Europe (8). The vaccine tested in this trial was designed to target the two types of HPV that cause the most cases of cervical cancer: HPV-16 and HPV-18 (8). Over one thousand women took part in the Phase II trial and have been tracked by researchers for four and a half years (2,6). The vaccine was found to be extraordinarily effective against the target types of HPV. It showed 100% efficacy against persistent HPV infections (6) as well as cytologic abnormalities (abnormal Pap tests) and cervical precancers, called CIN (2). This was a great success for the researchers, who, when the study began, hoped for 60-70% efficacy (2). Results published in April 2006 indicated that the vaccine remained 100% efficacious against HPV 16 and 18 up to 4.5 years after the vaccine was administered (10). The vaccine contains "virus-like-particles" (VLPs) (6), which use the outer coat of the virus to promote the development of an extremely effective immune response against this signal (2).

The development of this vaccine will revolutionize gynecological healthcare. The Pap smear was once the only way of combating cervical cancer, but with the advent of this vaccine, Pap testing and vaccination together can powerfully prevent and detect precancers at early, curable stages. Additionally, the per dollar benefit of a vaccination/Pap program is far greater than that a Pap screening program alone (2).

The vaccine was developed at the National Institute of Health, but tested in human trials through two pharmaceutical companies because the costs of its development were too high for federal funding (2). In 2004, GlaxoSmithKline reported that "investigators at more than 90 sites in 14 countries around the world are currently seeking to enroll approximately 13,000 women aged 26-45 years as volunteers to participate in a 3-year phase III study, which is aimed at evaluating the safety and efficacy of the new cervical cancer vaccine" (11). Throughout the testing phase of research for the vaccine, women in the Upper Valley have been very involved in the study (2). The particular vaccine researched by Dr. Harper in the trial she directed may be sold by GlaxoSmithKline as Cervarix as early as 2007, has efficacy against the two most common HPV types (16 and 18) and, surprisingly for the research team, also has complete efficacy against the next two most common cancer-causing HPV types (31 and 45), making this vaccine protective against 4 of the 15 types that cause anogenital cancers (2, 8). Upper Valley women have also, under the direction of Dr. Harper, enrolled in the Merck HPV vaccine trials. Merck will release an HPV vaccine that targets two non-cancer causing types of HPV that cause genital warts, in addition to targeting HPV 16 and 18 (12). Merck's vaccine, called Gardasil, is expected to be approved by the FDA in June of 2006, and on the market in the late fall of 2006 (13).

The ability to effectively vaccinate against cancer is astounding, but there are still some hurdles that remain in implementing a large-scale eradication of the virus that causes cervical cancer. One hurdle the makers of the vaccine must clear is the assessment of the Advisory Committee on Immunization Practices (14). Without endorsement from this group, it is unlikely that the vaccines will succeed (14). The vaccine faces a particular challenge because it is viewed as a vaccine for a sexually-transmitted virus, though in reality HPV is very different from a STI. Since the vaccine has to be administered prior to exposure, the recommended age for vaccination would be around 15 (2). There was initial opposition, especially from Christian groups, that the vaccine may encourage sex among young adults (14); this objection has dissipated due to the obvious benefits of cancer protection (2). However, the vaccine could be used to inoculate women of any age against cervical cancer (2). Another issue is that of vaccinating boys as well as girls. Since men are not able to develop cervical cancer, but may carry HPV, and develop anal and penile cancers, vaccinating males may proceed alongside vaccination of females. Tests of the vaccine on men have been successful (2).

Despite these controversies, hopes remain high for the vaccines against HPV. As Dr. Harper states, "smallpox is a small DNA virus – HPV is a small DNA virus; small pox infected only the skin – HPV infects only the skin; small pox has been eradicated through vaccination – HPV may be eradicated through vaccination. This is the biggest healthcare advance in 50 years for women" (2). Perhaps coming generations will no longer have to fear at least one type of cancer—a truly remarkable achievement.

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