Gynecologic Cancer Prevention Research at DHMC

The most common viral sexually transmitted infection, Human Papillomavirus (HPV), directly causes 99% of all cervical cancers (Im 322). In the United States, the incidence of HPV is rising at a staggering rate, with 75% of sexually active adults exposed to HPV. Women between the ages of thirteen and twenty eight show an especially high prevalence rate of 40%, and on college campuses alone there exists a 43% prevalence rate (Hagensee 19). For women worldwide, cervical cancer is the second most common cancer, killing 200,000 and infecting 450,000 more each year.

Unfortunately, the current treatment for cervical cancer is often unsuccessful. Diane Harper, M.D. of the Obstetrics and Gynecology Department of Dartmouth-Hitchcock Medical Center (DHMC) has witnessed its shortcomings firsthand. "In my early years here at Dartmouth as a faculty member, I had a seventeen-year-old patient who had already undergone fiveleep procedures (excision of the cervix to remove the lesion and reduce potential reoccurrence of HPV and cancer);" Harper revealed during an interview with the DUJS.

Questioning how the medical community could do better, Harper began to search for other means of treating patients more effectively and improving the quality of patient care. Motivated by inadequacies with current treatments, Harper accepted the responsibility of finding a better method for treating women with cervical cancer. In 1997, as Director of the Gynecological Cancer Prevention Research Group at DHMC, Harper joined in the worldwide effort to create a vaccine against HPV by launching the only east coast clinical research site in conjunction with pharmaceutical maker Merck & Co, Inc.

Since then, the Merck clinical research study on HPV and cervical cancer has produced promising results. In November 2002, the New England Journal of Medicine published the preliminary results of the study: Merck's vaccine against HPV type 16, which is responsible for more than 50% of cervical cancer cases, proved 100% effective in eliminating the risk of infection while producing no serious side effects (Schultz 102). Dartmouth was one of the eleven national sites to submit samples that were completely successful. Following this success, Dartmouth's Gynecological Cancer Prevention Research Group has begun conducting the final stages of the trial, which will continue over the next four years. If the results confirm those of last year, the Food and Drug Administration (FDA) will approve the vaccine, making cervical cancer the first cancer to be prevented by a vaccine.

In the early 1990s, virus-like particles of the Human Papillomavirus were discovered and fabricated in the laboratory. The fundamental component of the vaccine, virus-like particles are essentially empty virus capsids that contain only the major HPV capsid antigen and not the viral DNA. Thus, the virus-like particles cannot spread infection. Rather, they induce the body to initiate an immune response by imitating the L1 protein, the major capsid protein for HPV, and the one that induces antibody responses and defense mechanisms in the body (Schultz 102). The virus-like particles in the HPV vaccine are based on the L1 protein, the major capsid protein for HPV, and the one that induces antibody responses and defense mechanisms in the body (Bosch 179).

After developing the vaccine, Merck scientists proceeded with the first phase of the trials by conducting preliminary toxicity experiments on animals. Rather than focusing on efficacy, the drug's tolerability and potential were the main objectives during this early stage. With the results judged satisfactory by the FDA, the study advanced, and testing began on a small human population. Due to the risks involved, this initial human study was carefully regulated, and the volunteers were closely monitored for organ failure, autoagulation problems, and other potential complications. The objective of these Phase 1 (dose-escalating) trials was to determine the maximum quantity of the drug that could be tolerated by individuals. Once the FDA established a tolerability level, the study moved into the next phase. Phase 2 of the study began in 1997 at Dartmouth. Harper sought the aid of her colleague Walter Noll, M.D., Director of Molecular Diagnostic Laboratory, to serve as an expert in laboratory analysis. Together, they prepared for the clinical vaccine study by integrating Noll's knowledge of HPV laboratory testing into the epidemiological studies that Harper was conducting during that time.

After laying the groundwork, the DHMC Gynecological Cancer Prevention Research Group recruited approximately 1,500 female participants ranging from sixteen to twenty three years of age from the Dartmouth community. In contrast to the first phase, the primary objective of this "proof-of-principle" stage of the study was to determine the vaccine's efficacy. To test if the vaccine indeed prevented HPV infection, Phase 2 examined only HPV type 16, targeting the factor responsible for more than 50% of all cervical cancers (Im 322). Tested against the placebo control, which was allocated to roughly half of the participants, the monovalent type 16 vaccine underwent various tests for infection rate, dose, safety, and side effects. To test the vaccine's efficacy, the lesions that occur as a result of other HPV types had to be identified and documented. The Roche Molecular System was employed for this purpose. This polymerase chain reaction (PCR) amplification device uses the L1 primer system and a reverse line blot detection strip to categorize each HPV type individually. Using the Roche system, a biopsy tissue sample was collected from the main 29 HPV types. When a particular HPV type is present, the corresponding detection strips will appear dark. The percentage of lesions in cohorts will serve as the indicator of the effectiveness of the vaccine. Impressively, the combined results of Phase 2 from Dartmouth and the ten other sites indicated 100% efficacy of the vaccine.

In addition to this national finding, the Dartmouth site independently produced results concerning a new method of obtaining cervical samples. Recently developed by the DHMC Gynecological Cancer Prevention Research Group, this new self-sampling method enables women to evaluate themselves via a long, Dacron covered swab Q-tip. This eliminates the need for a speculative exam in the clinic. In the fall of 2002, Harper demonstrated the DHMC's latest advancement in sampling methods. According to the results obtained from the 1,500 Dartmouth patients, self-sampling proved to be equivalent, if not superior, to speculative exams because of the ability to obtain samples covering a greater region of the cervix. In contrast to self-examination for breast cancer, the self-sampling option will improve preventive care tremendously by detecting HPV earlier and more frequently in addition to being more convenient. Encouraged by these results, other research studies are also starting on a self-sampling method instead of in-clinic examinations (personal communication).

Supported by such promising results, the vaccine against HPV has now entered into its final four-year phase, the last step before it can acquire official FDA approval and be marketed. With more than 15,000 participants covering the six major continents, Phase 3 aims to validate the previous efficacy results using a larger population and to ensure the absence of adverse side effects on the particular subpopulation. Also, the scope of this phase will be extended beyond the monovalent type 16 vaccine to include the quadrivalent vaccine (types 6, 11, 16, and 18).

If the results of Phase 3 are successful, the vaccine will prove to be an efficient preventive strategy against cervical cancer and will have a tremendous impact on women worldwide (Bosch 183). The monovalent type 16 vaccine itself is projected to eliminate at least 50% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths. Health regulating committees such as the World Health Organization are expected to follow the decision of the FDA and approve the vaccine. This would be particularly significant as it would lead to the distribution of the vaccine at a reduced cost in developing countries to women, who account for 80% of all cervical cancer deaths.

While these results are obviously very promising for the vaccine's future, these studies and Dartmouth's Gynecological Cancer Prevention Research Group have already made a significant contribution to the fight against HPV. Dartmouth's research has also made a significant number of women in the New Hampshire/ Vermont region that enrolled in the study have been protected from HPV by the vaccine. In addition, the Gynecological Cancer Prevention Research Group has successfully curbed the spread of infection by actively
conducting educational seminars on campus in order to raise awareness of HPV.

As one of the leading cervical cancer detection research teams in the country and the first to develop the practice of self-sampling for HPV in the United States, the Gynecological Cancer Prevention Research Group has placed DHMC “on the map” and continues to provide a significant contribution to scientific literature. Through the dedicated work of researchers worldwide, such as those at the Dartmouth’s Gynecological Cancer Prevention Research Group, the vision to eliminate cervical cancer has already become a reality.

REFERENCES


DUJS Submission Guidelines

What are we looking for?

The DUJS is open to all types of submissions. We examine each article to see what it potentially contributes to the Journal and our goals. Our aim is to attract an audience diverse in both its scientific background and interest. To this end, articles generally fall into one of the following categories:

Research

This type of article parallels those found in professional journals. An abstract is expected in addition to clearly defined sections of problem statement, experiment, data analysis and concluding remarks. The intended audience can be expected to have interest and general knowledge of that particular discipline.

Review

A review article is typically geared towards a more general audience, and explores an area of scientific study (e.g. methods of cloning sheep, a summary of options for the Grand Unified Theory, etc). It does not require any sort of personal experimentation by the author. A good example could be a research paper written for class.

Reflection

A reflection article resembles a popular science article or an editorial. It can examine the interplay between science and society, recall the experiences of your failed summer research, or comment on how you perceive the scientific community. These articles are aimed at a general audience and should include explanations of concepts that a basic science background may not provide.

Technical guidelines

1. The length of the article must be 3000 words or less.
2. If it is a review or a research paper, the article must be validated by a member of the faculty. This statement can be sent via email to the DUJS account.
3. Any co-authors of the paper must approve of the submission to the DUJS. It is your responsibility to contact the co-authors.
4. Any references and citations used must follow the American Psychological Association (APA) guidelines.
5. If you have chemical structures in your article, please take note of the American Chemical Society (ACS)’s specifications on the diagrams.
6. PROOFREAD, PROOFREAD, PROOFREAD. Please run your article through spellcheck prior to submitting it.

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