# Patients As Subjects For Research: Ethical Dilemmas For The Primary Care Clinician-Investigator

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***Background*: Past studies suggested an association between human papillomavirus (HPV) and cervical intraepithelial neoplasia (CIN). In 1987, University of North Carolina (UNC) Hospitals Family Practice Center clinicians were approached for a control population to study this association.**

***Methods*: One hundred five patients attending the UNC Hospitals Neoplasia Clinic with biopsy-proven CIN 2 or 3 and 268 control patients attending the UNC Family Practice Center for a routine Papanicolaou smear were enrolled in this case-control study. Case and control patients consented to having an additional cervical specimen taken and to being interviewed. The cervical specimens were classified by the Southern blot and polymerase chain reaction techniques for HPV.**

***Results*: Early results suggested the control patients who had HPV were at high risk of developing CIN. Interventions were made to inform these patients of this risk and need for closer follow-up, causing a wide range of patient reactions. The final results showed no association of HPV with CIN, indicating the early interventions were premature.**

***Conclusions*: Physicians engaged in research need to be prepared to deal with the discovery of health risks in the otherwise "normal" control patient. They bear the ethical responsibility of scrutinizing study design and methods and planning communication with patients from the inception of a study. (J Am Board Fam Pract 1994; 7:196-201.)**

Primary care populations are often the source of control groups for epidemiologic studies.[1] Subjects might be recruited through advertising, hospital clinics, or solicitation by office-based primary care providers. Often these clinicians are facilitators of the specific project being implemented and might or might not have been involved in the design or development of data instruments and consent forms. These clinicians are usually aware of the basic criteria used for assessing the ethics of biomedical research.[2] The Declaration of Helsinki (1964) noted that human studies must follow accepted scientific principles using approved experimental protocols and investigating medically relevant issues. The potential benefit of the study must outweigh the assessed risks to the subjects being studied. The declaration continued: "In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits, and potential hazards of the study and the discomfort it may entail."[3]

Ethical issues in biomedical research were clarified by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, published in 1983.[4] The commission defined informed consent "as a process of shared decision making rather than a scientific ritual," in which patients are provided with information about a study in language they can understand.

The institutional review board of a research institution is responsible for evaluating and putting its stamp of ethical approval on the design, methods, and informed consent of a study.[5] The ability of an institutional review board to judge is dependent on the scope of presentation by the investigators and the expertise of the institutional review board members.

While these codes and guidelines and the institutional review board provide a basic ethical framework for biomedical research, the primary care physician who enlists patients to participate is responsible for applying these general principles to the specific demands of a study. The primary care physician should approve the research design, obtain informed consent, and assess possible beneficial and deleterious effects of partic-

Submitted, revised, 7 January 1994.

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pation in the study.[6] The potential of negative consequences for a patient presents a conflict of interest for the physician, whose primary role as a physician is to enhance the well-being of the patient, while as a researcher the role is to uncover relevant knowledge for the general good.[7] Control populations, although necessary in medical research, can be subject to inherent risks; even epidemiologic research might result in the discovery of a clinically important medical problem in a "normal" control patient.[5] The physician-researcher might also deal with a conflict of interest when the physician or patient receives financial incentives for participating in research.

In 1987 the physician authors (SFS, PC) were approached by an epidemiologist (AC) interested in the association and possible causative role of human papillomavirus (HPV) in the development of cervical intraepithelial neoplasia (CIN).[8-10] The epidemiologist was seeking a control group of patients to compare with women who had CIN. This report describes how this study, which was conducted in our medical practice, raised a number of ethical issues and logistical problems and how these were addressed.

## Methods

This study was designed to assess the role of human papillomavirus (HPV) DNA types 16, 18, and 31 in the development of CIN levels 2 and 3, controlling for known and suspected risk factors for CIN. One hundred five women attending the UNC Hospitals Neoplasia Clinic (from 1 September 1987 to 8 November 1988) who were found to have biopsy-proven CIN 2 or 3 were consecutively enrolled in the study. Two hundred sixty-eight control women were recruited as they came to the UNC Hospitals Family Practice Center (September 1987 to November 1988) to receive routine Papanicolaou smears. All control patients had normal findings on cytologic examination of cervical smears.

Before recruiting any control patients, the epidemiologist (AC), who was the principal investigator, presented the study design to the clinicians of the Family Practice Center, who agreed to participate. Two liaison clinicians on the staff of the Family Practice Center, including one of the authors (SFS), were assigned responsibility for communicating with the physicians and staff about the study and handling of related patient care issues.

Individual patients were recruited into the study by staff or providers as they registered at the UNC Family Practice Center for their appointments for Papanicolaou smears. The principal investigator then obtained informed consent and assisted the nursing and laboratory staff in handling the additional specimens obtained for HPV detection. The HPV DNA type was determined using the reference standard for HPV DNA classification at the time of the study, namely, the Southern blot technique.[11]

Informed consent for participation was solicited from case and control subjects to permit collection of the additional cervical smear for study and to be interviewed. The consent form was approved by two institutional review boards (School of Public Health and School of Medicine). The form indicated to patients that they were involved in a research study investigating factors that might influence a woman's chance of developing abnormal cells in her lower genital tract. HPV was not specifically mentioned in the consent form.

After their examinations all case and control subjects were interviewed in person or by telephone to collect information on possible other risk factors of CIN, including age, education, sexual and reproductive histories, cigarette exposure, sexually transmitted disease history, and use of birth control methods.

The HPV classification and analysis of data were conducted in batch form at six intervals during the study period.

## Results

The study took place during approximately 2 years, with patient recruitment and specimen collection occurring from September 1987 through November 1988 and specimen and data analysis being conducted through July 1989. The results were assessed at intervals of 2 to 6 months and are shown in Figure 1. In January 1988 after 5 months of the study, preliminary data showed a statistically significant odds ratio of 34.0. Women with CIN 2 or 3 were 34 times more likely to be HPV 16, 18, or 31 positive compared with the control group. This odds ratio was based on small numbers (18 cases positive for HPV 16, 18, or 31).

These early findings, as well as findings from earlier studies in the medical literature, suggested an association between HPV 16, 18, or 31 and CIN.[8-10] The Family Practice Center liaison

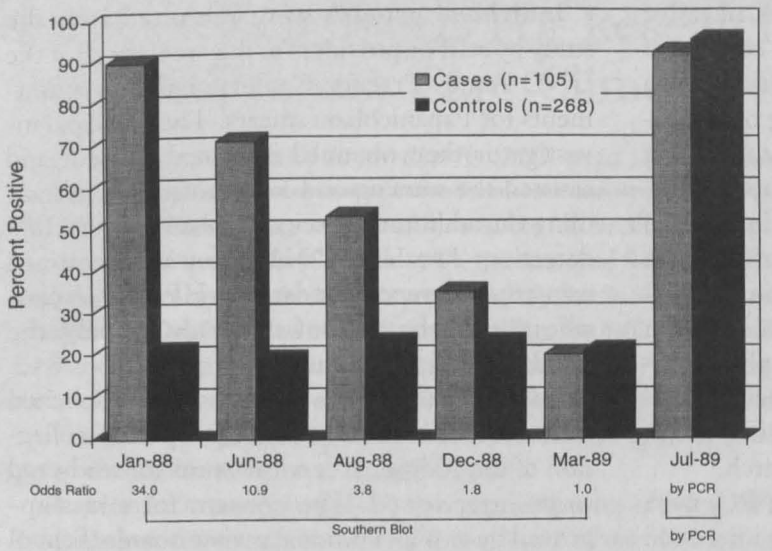


**Figure 1. Odds ratio changes in percentage of women positive for human papillomavirus 16, 18, or 31 from January 1988 through July 1989. (Note: The sample size increased across the study period.)**

clinicians became concerned that the control patients positive for HPV 16, 18, or 31 were at risk for rapid development of CIN.[12] The liaison clinicians met with the study investigators and consulted gynecologic oncologists. As a result, a decision was made to contact HPV 16-, 18-, or 31-positive control patients to inform them of their HPV status and recommend closer monitoring with Papanicolaou smears at 6-month intervals. The oncologists also proposed referring these patients for colposcopy. The latter option was an intervention that went far beyond the approved study protocol. The possible need for colposcopy had never been raised with the control patients, nor had study funds been allocated to pay for this procedure. Finally, the effectiveness of treating HPV to prevent the development of cervical cancer was not validated in the medical literature at that time.[13]

The family practice liaison clinicians and the study investigators concluded it was best to contact the HPV 16-, 18-, or 31-positive control patients by telephone, as well as to notify their personal physicians. The telephone call was to be documented on the woman's medical record, stating that HPV 16, 18, or 31 had been identified on a cervical specimen and that Papanicolaou smears were advised every 6 months.

During the ensuing months the liaison clinicians contacted 35 HPV 16-, 18-, or 31-positive women and informed their personal physicians. At that time there was also extensive national coverage regarding HPV as a causative agent for cervical cancer.[14,15] A wide range of issues was raised by the subjects, including the seriousness of HPV infection, pathogenesis, mode of transmission, prognosis, potential therapy, risk to sexual partners, and effects on childbearing. The women's reactions ranged from gratitude for being made aware of a problem to bewilderment, panic, and anger. Universally they were concerned about the potential risk to their health. One woman was denied health insurance because of documentation of HPV infection in her medical record.

The process of communicating HPV positivity was particularly disconcerting for the liaison clinicians, who had to convey information about a health risk for which there was much publicity but little definitive prognostic and therapeutic information.

One year after the study began (August 1988), a cumulative data analysis indicated that the odds ratio for HPV 16, 18, or 31 to be present in cases versus controls had dropped from 34.0 to 3.8. This level of association suggested that controls with HPV 16, 18, and 31 were not at an alarmingly high risk of developing CIN, and efforts to contact these patients were slowed. At the conclusion of the study (March 1989), the cumulative odds ratio was 1.0. The study concluded that women with CIN 2 or 3 (cases) were no more likely to be infected by HPV 16, 18, or 31 than were women with normal findings on Papanicolaou smears (controls) and that HPV was not a significant risk factor for CIN.[16] The study did show, however, that smoking, early age of sexual activity, and multiple partners were statistically significant risk factors for cervical neoplasia.

Toward the end of the study all of the original cervical specimens were reclassified for HPV using the new highly sensitive polymerase chain reaction (PCR) technique.[17] Ninety-five percent of the control group and 92 percent of the women with CIN 2 or 3 were positive for HPV 16, 18, or 31, an odds ratio approaching 1.0. This high positivity was probably the result of the excess sensi-

tivity of the PCR test. The investigators concluded that the PCR results also demonstrated a lack of association between HPV and CIN; therefore, there was minimal risk for CIN to the family practice control patients who had normal Papanicolaou smear results and HPV 16, 18, or 31.

All the study investigators and liaison clinicians met at the conclusion of the investigation and, in consultation with gynecologic oncologists, approved that all the control patients be sent a letter explaining the results of the study. These women were advised that annual Papanicolaou smears constituted adequate follow-up, regardless of their HPV status.

Since the conclusion of the study, much has been learned about HPV. Evidence is now strong that there is a cause-and-effect relation between HPV 16, 18, and 31 and cervical neoplasia.[18] It is likely that, at the time of this study, both the Southern blot and PCR technologies were not sufficiently reliable to identify HPV subtypes accurately.

## Discussion

The issues facing the primary care clinicians in this study are generally applicable to office-based studies. The responsibilities of physician-researchers vary with their roles in research. They may serve as principal or co-investigators or as recruiters of patients. Primary care physicians who are undertaking their own research or are co-investigators must assume responsibility for a valid and reliable study design and communication with study participants. For the patient recruiter, the study design, consent form, and protocols are usually prepackaged without regard to the characteristics of individual clinical practice. Nonetheless, this research experience underscores the need for family physicians serving as liaisons or patient recruiters to understand and scrutinize study design and results.

### *Study Design*

At the beginning of a study, the primary care physicians must clearly understand the reliability and limits of the chosen scientific techniques, including research design and laboratory testing. In our study the primary care liaisons were not expecting to deal with several aspects of the study design. They were unaware that there was a question of reliability in the Southern blot and polymerase chain reaction tests. They were not prepared for the possibility of discovering adverse results in the control patients during the early course of the study. In fact, it was probably inappropriate to convey to patients the results of preliminary analysis based on the still experimental Southern blot test.

The preliminary data seemed to confirm the prevalent theory that HPV types 16, 18, and 31 were oncogenic. The pathogenic role of HPV in cervical cancer was also fueled by reports in the national press. As researchers, the primary care liaisons should have waited and not intervened until the study was completed, but as clinicians, they felt obligated to care for their patients who were in possible danger. This conflict of interest between carrying out a research protocol and caring for the patient's individual needs is echoed by both Freedman[2] and Pocock.[19] Using an independent data-monitoring committee who is the sole bearer of ongoing study results has been proposed. Such an independent committee would prevent intervention by investigators before the conclusion of a study because of discovery of a superior therapy in clinical trials or significant laboratory findings in epidemiologic studies, such as the one described, unless mandated by the committee.[2,19]

A secondary consequence of discovering a potentially serious medical problem in a study subject is the loss of anonymity, though hopefully not confidentiality, in identifying the subject at risk and then advising medical management.[20] Unless the specific adverse outcome is anticipated during the design of the study, neither consent nor protocol will be able to address documentation of this patient's newly discovered medical problem in the medical record, treatment, or referral.

Phillips and Vazquez[21] have illustrated with individual cases the issues raised by the discovery of abnormal laboratory findings in normal or control research subjects. They acknowledged the lack of guidelines for dealing with an unexpected adverse finding in a control patient and the emotional distress suffered by both the subject and researcher. They discussed the legal responsibility and liability of the clinician-researcher to notify the subject of the abnormal result and the need to maintain confidentiality, unless a disease that could pose a threat to a third party is uncovered.

### *Communicating Results*

For potential subjects a consent form should provide an accurate description of the project to the patient. The consent form must delineate what will happen in the study, as well as its benefits and potential risks, including the detection of unexpected abnormalities.[21] The unknown role of HPV among other potential factors in the development of CIN was the topic of this investigation. Thus, HPV was not specifically described in the consent form, as approved by two institutional review boards. All possible outcomes, especially for the control patients, had not been worked through by the liaison clinicians and therefore were not included in obtaining consent. In retrospect both patients and clinicians would have been better prepared to deal with the eventuality of the HPV-positive control patient by reviewing and playing out scenarios of potential results.

Primary care physicians who undertake or collaborate in research studies often believe it is important to communicate the results to their patients and colleagues in practice. In the study presented here, the preliminary data carried implications that generated considerable positive and negative feelings in the patients contacted by the liaison clinicians. Recommendations for more frequent follow-up with Papanicolaou smears had been neither planned nor financed. A study by Wilkinson, et al.[22] investigating the anxiety produced when informing women by mail about abnormal Papanicolaou smear results found that anxiety was significantly reduced by enclosing literature that addressed the importance of the abnormal cells seen on the Papanicolaou smear. Unfortunately, literature on the significance of a positive cervical probe for HPV was nonexistent at the time of the described study. Final data analysis showed no evidence that HPV was an oncogenic risk factor in the study population. Communicating this finding was both a relief and an embarrassment that has remained with the study liaison clinicians. They continue to care for these study patients and to practice with the same colleagues. Unlike professional researchers, they did not move on to the next project with another study population.

The authors hope that this report will not deter primary care physicians from initiating or participating in clinical research. Primary care needs investigation and validation. Clinicians should seek guidance and advice from more than one source when assessing a proposal and evaluating methodology and laboratory techniques. With the assistance of all investigators and experts involved, the primary care clinician-researchers need to plan communications from the beginning of a study. They must prepare a consent form that incorporates possible outcomes. They must plan responses to patient and clinician questions and devise methods of debriefing or informing participants of study results. As suggested by Brett and Grodin,[23] ongoing quality assurance and evaluation throughout the course of a study are essential to assure both excellent patient care and ethical research.

In summary, family physicians who serve as liaisons in research have an ethical responsibility to understand the study design and maintain careful communication with patients who are subjects.

For their collaboration and advice, the authors thank Ms. Jacki Resnick; Paul Dunn, FNP; and the patients, staff, and physicians at the Family Practice Center, University of North Carolina Hospitals at Chapel Hill, NC.

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