CASE STUDY

Observational study of cervical cancer

FROM: *CASEBOOK ON ETHICAL ISSUES IN INTERNATIONAL HEALTH RESEARCH*

> Although this case study is based on research that took place in the 1970s, the questions that it raises remain relevant today.

Cervical cancer causes at least 273 000 deaths globally every year, and about 85% of these deaths occur in developing countries. The incidence of invasive cervical cancer has decreased in countries where women have access to regular Papanicolaou (Pap) smears(1) and subsequent treatment of pre-malignant cervical dysplasias(2) readily available. Most often, women with fatal cases of cervical cancer have never had a Pap smear or have to wait long intervals between Pap screenings.

Cervical dysplasia ranges from low grade squamous intraepithelial lesion (SIL) to high grade SIL.(3) The next stage is carcinoma in situ, indicating that although cancerous cells are present they have not yet spread. In the 1970s, there was lack of consensus in the medical community about which types of dysplasia would progress and become cancerous. Many countries with adequate health facilities took an aggressive position and treated early dysplasia. In many developing countries, however, decisions about when to treat were guided by the belief that not all dysplasias progress to cancer, and this position was supported by previous studies of the natural history of cervical cancer. Thus, in developing countries the most widely accepted stage at which to begin treatment was that of carcinoma in situ, indicating that the cells had become cancerous but remained limited to the cervix.

If doctors could more accurately predict which dysplasias would progress to carcinoma in situ, they could be more specific in deciding which cases to treat early. The development of a more precise diagnostic method that could detect whether a dysplasia was of the type that progresses to cancer would save money and ensure that more women would receive treatment. To design guidelines for a national control programme for cervical cancer, the national medical research council of a South Asian country funded an observational study of cervical cancer to determine which dysplasias were most likely to progress to cancer.

The study, approved by the research ethics committee of the research council, took place over 12 years, beginning in the mid-1970s. Eight government hospitals in one of the country's major cities participated. Most of these hospitals provided both general and specialized gynaecological care but were busy and did not have adequate facilities to manage patients with cancer. Patients with cancer were, therefore, referred to the nearest regional cancer centre for treatment and follow up, with a standard 6-month waiting period to begin treatment.

The researchers elicited the help of community health workers to inform women about the study and encourage them to go to the city hospitals for Pap smears. Women who presented at the eight government hospitals were informed about the study, and were asked to give a Pap smear with informed consent. Since most women in the study were illiterate, the researchers provided information in simple, non-medical language and obtained verbal consent. The researchers did not inform the women that their lesions might progress to cancer. Women were not made aware that treatment was available.

By the ninth year, researchers had identified more than 1000 women with varying degrees of cervical dysplasia. Women found to have a positive Pap smear at intake were followed up every 3 months, to record the progression of their disorder on the basis of the Pap smear. The end-point for treatment was defined as the development of carcinoma in situ, at which time they were referred to the nearest regional cancer centre, which had a very long waiting list. By the time some of these women were seen by an oncologist, the lesion had progressed to a higher level.

Midway through the study, a leading North American medical journal published the results of a longitudinal study of cervical cancer. The study concluded that cervical dysplasia was a precursor for cervical cancer, and thus that all forms of dysplasia warranted treatment. Despite these new findings, the researchers continued with the study. By the end of the study, 71 women had developed malignancies. In nine of these women, the disease had already spread to other parts of their body. The research team provided no treatment to the women once the study had ended.

Questions

1 Discuss the ethical issues raised by this observational study.

2 Given the shortage of staff, facilities, and equipment in the government-run hospitals, was the medical research council justified in conducting this study? Could national guidelines have been set up without conducting this study?

3 Should continuing services have been offered to participants after completion of the study? If so, what services should have been offered?

4 Does diagnosing a condition or disease during research result in a duty (obligation) to provide care and follow-up for that condition? Is this duty the same whether the condition is diagnosed to include patients in the study or to exclude them?

5 Do the researchers have any responsibility to "take stock" of the situation at least mid-way through such longitudinal studies? Should the sponsors ask for such an evaluation?

6 Should this study have had some stopping rules, or a monitor?

7 Should this study be accepted for publication? If not, how should the results of this study be made generally known to others?

Notes:

(1) A routine screening test used for the detection of early cervical abnormalities, namely precancerous dysplastic changes of the uterine cervix, together with viral, bacterial, and fungal infections of the cervix and vagina. Cervical screening is a relatively simple, low-cost, and non-invasive method. Regular screening for cervical cancer reduces both the mortality from and incidence of cervical carcinoma.

(2) Abnormal development or growth of tissues, organs, or cells. It is the earliest form of precancerous lesion. Dysplasia can be diagnosed as either high or low grade, with high grade dysplasia indicative of a more advanced progression towards malignant transformation.

(3) A general term for the abnormal growth of squamous cells on the surface of the cervix. The changes in the cells are described as low grade (LSIL) or high grade (HSIL), depending on how much of the cervix is affected and how abnormal the cells are. HSIL is regarded as a significant precancerous lesion, whereas low-grade SIL (LSIL) is more benign, since most of these lesions regress.

CASE STUDY RESPONSES

Knowledge vs ethics in clinical research in resource-poor settings: a clinician's perspective

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This case study of the 1970s (1) no doubt raises several ethical questions. I will however try to look at the case study from the perspective of a gynaecologist and primary care physician attempting to establish a community-based cervical cancer screening and care programme in rural Tamil Nadu.

There is enough knowledge today that cervical cancer is caused by the Human Papilloma Virus and progresses through stages of cervical intraepithelial neoplasia (CIN), carcinoma in situ (CIS) to invasive cervical cancer. This knowledge determines the modalities of screening and treatment recommended today for cervical cancer and its precursors. However, while attempting to analyse the case study to draw lessons for current practice, one needs to start from the scientific evidence that was available regarding cervical cancer precursors at the time of the study, to consider whether a study to understand the natural history of cervical cancer was necessary, and whether the study was justified in its design of following up women with proven dysplasia without any intervention, given the evidence available at that time.

Since I have no personal knowledge of the clinical scenario in the period of the study, I looked through literature on the history of cervical cancer treatment and also spoke to two senior gynaecologists who were working in premier medical institutions in India at that time. I understand that the progressive nature of cervical dysplasias (as they were called then) to cervical carcinoma was well known by the early 1970s. In 1968, Richart (2) indicated that all dysplasias have the potential for progression. However, there seems to have been a lack of clarity on how exactly each grade of dysplasia behaved and what proportion actually progressed to invasive cancer. This was an important issue, especially while evolving guidelines for treatment in high disease-prevalent resource-poor settings like India. Based on existing understanding, while carcinoma in situ was most often treated with hysterectomy, severe forms of dysplasia were often treated with an excisional cone biopsy of the cervix. Treatment for mild and moderate dysplasia did not seem to have any standard protocol and varied between individual facilities. Answers to questions