HPV AND CERVICAL CANCER

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INTRODUCTION

- CERVICAL CANCER IS THE SECOND MOST COMMON CANCER IN WOMEN WORLDWIDE AND THE COMMONEST IN WOMEN LIVING IN AFRICA
- IN 2000 IT WAS ESTIMATED AT EACH YEAR APPROXIMATELY 493 000 WOMEN DEVELOP CERVICAL CANCER AND 274 000 DIE FROM THE DISEASE, WITH 83% OF ALL CASES OCCURRING IN LOW-RESOURCE COUNTRIES

- CERVICAL CANCER AFFECTS WOMEN IN THE FIFTH AND SIXTH DECADES OF THEIR LIVE, WHEN THEY PLAY A CRITICAL ROLE IN THEIR FAMILIES, COMMUNITIES, AND WORKPLACE.
- HUMAN PAPILLOMA VIRUS (HPV) HAS A CRITICAL CARCINOGENIC ROLE IN CERVICAL CANCER DEVELOPMENT.

HORIZONTAL TRANSMISSION

- HPV DNA HAS BEEN DETECTED IN THE NAIL BRUSHES OF 3 OF 8 WOMEN WITH CERVICAL HPV.
- HPV DNA HAS BEEN DETECTED IN THE NAIL BRUSHES OF 9 OF 13 MEN WITH PENILE HPV INFECTION.
- PATIENT WITH GENITAL WARTS MAY TRANSFER GENITAL HPV NOT ONLY TO THEIR SEXUAL PARTNERS BY GENITAL-FINGER TRANSMISSION, BUT ALSO HORIZONTALLY TO THEIR CHILDREN BY TOUCHING THEM.

TRANSMISSION VIA BLOOD, BREAST MILK AND SPERM

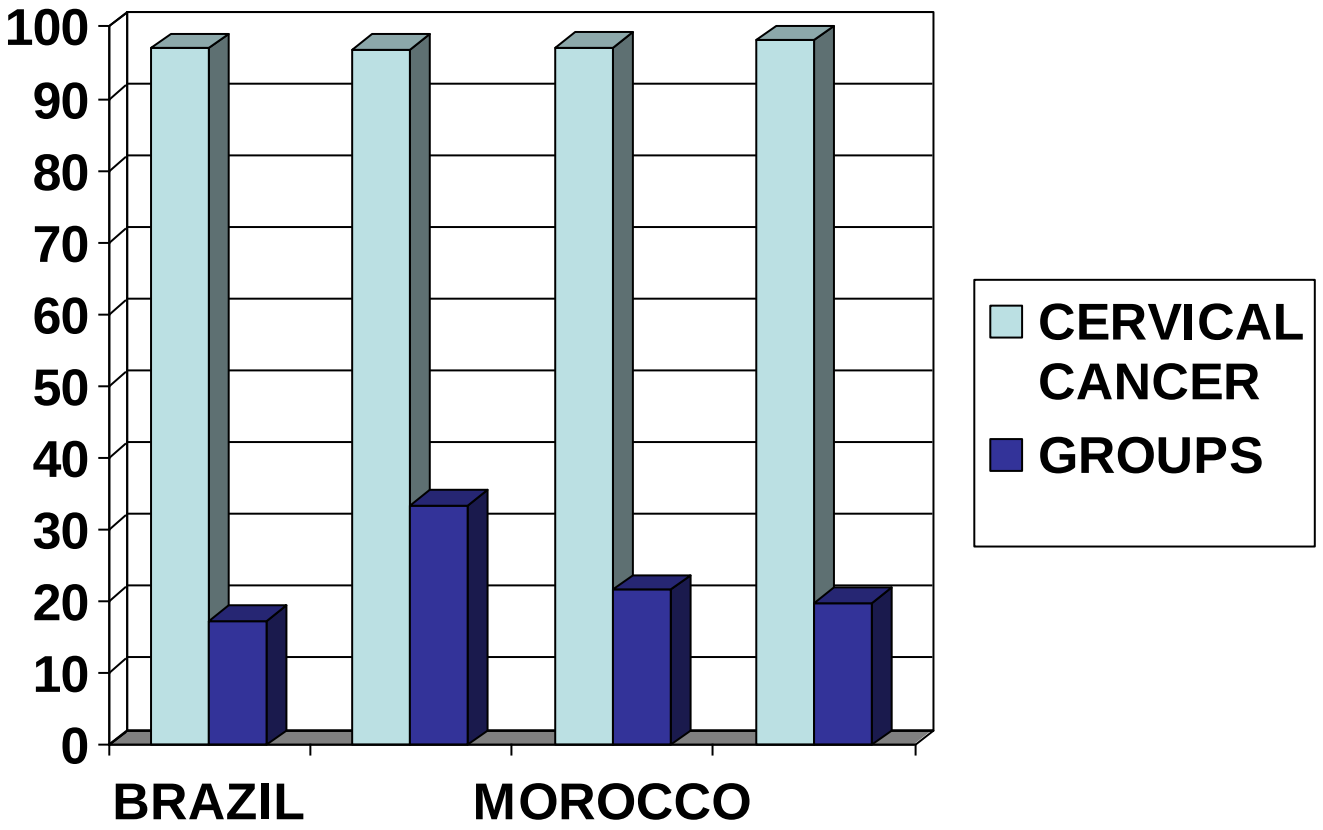
- NO HPV HAS BEEN DETECTED IN BLOOD.
- TRANSMISSION HPV TO INFANT VIA BREAST-FEEDING HAS NOT BEEN DOCUMENTED.
- THE SOURCE OF HPV IN SEMEN IS FROM URETHRAL EPITHELIAL CELLS.

THE PREVALENCE OF HPV DNA IN CERVICAL CANCER SPECIMENS

- THE RELATIONSHIP BETWEEN HPV INFECTION AND CERVICAL CANCER HAS BEEN RECOGNIZED IN A LARGE BODY OF STUDIES, AND DETERMINED AS CAUSAL BY INTERNATIONAL REVIEWS SINCE THE EARLY 1990s.

- STATE-OF-THE ART AMPLIFICATION TECHNIQUE USE IN CASE-CONTROL STUDIES, CASE-SERIES, AND PREVALENCE SURVEYS HAVE UNEQUIVOCALLY SHOWN THAT HPV DNA CAN BE DETECTED IN 90 TO 100% OF ADEQUATE SPECIMENS OF CERVICAL LESIONS WITH THE CONCLUSION THAT MOST OF THESE NEGATIVE RESULTS ARE PROBABLY FALSE NEGATIVES.

HPV FREQUENCY IN CERVICAL CANCER PATIENTS COMPARED TO THE GENERAL POPULATION



TRANSMISSION ROUTES OF HPV TO THE CERVIX

TRANSMISSION	RELATIVE IMPORTANCE
SEXUAL INTERCOURSE	VAST MAJORITY OF CASES (>99%)
SEXUAL CONTACT WITH INCOMPLETE PENETRATION OR NO PENETRATION	HAS BEEN DESCRIBED BUT RARE

- TRANSMISSION TO SKIN OR ORAL CAVITY HAS BEEN DOCUMENTED BUT WITHOUT CLINICAL CONSEQUENCES.
- STUDIES THAT HAVE COMPARED RISK FACTORS IN CIN3 AND INVASIVE CANCER HAVE NOT REPORTED SIGNIFICANT DIFFERENCES IN THIS LESION ASSOCIATION IN HPV OR IN THEIR EPIDEMIOLOGICAL PROFILE.

- THE POOL OF IARC STUDIES WAS LARGE ENOUGH TO PROVIDE TYPE-SPECIFIC RISK ESTIMATES FOR 18 TYPES OF HPV.
- RECENT INTERNATIONAL REVIEW CONCLUDED THAT THE EVIDENCE IS NOW SUFFICIENT TO CONSIDER HPV TYPES 16,18,31,33,35,39,45,51,52,56,58,59,68,73 AND 82 TO BE HIGH RISK CARCINOGENESIS.

- OTHER TYPES THAT ARE FOUND IN NEOPLASTIC SPECIMENS HAVE BEEN CLASSIFIED AS LOW RISK. THEY INCLUDE HPV TYPES 6,11,40,42,43,44, 54,61,70,72,81 AND CP6108.
- FROM IARC AND OTHER STUDIES HPV TYPES 26,53,66 ARE CONSIDERED OF UNCERTAIN RISK.

- THE MEDIAN INFECTION DURATION IS ABOUT 8 MONTHS FOR HIGH-RISK HPV TYPES AND 4.8 MONTHS FOR LOW- RISK HPV TYPES.
- HPV 16 TYPE TENDED TO PERSIST LONGER THAN OTHER HIGH RISK TYPES.

- FOLLOW-UP STUDIES INVOLVING WOMEN WITH OR WITHOUT CERVICAL ABNORMALITIES HAVE INDICATED THAT THE CONTINUOUS PRESENCE OF HR-HPV IS NECESSARY FOR DISEASE DEVELOPMENT, MAINTENANCE AND PROGRESSION TO CIN.

- 15 TO 30% OF WOMEN WITH HR-HPV DNA WHO ARE CYTOMORPHOLOGICALLY HEALTHY AT RECRUITMENT WILL DEVELOP CIN2 OR CIN3 WITHIN THE FOLLOWING 4 YEARS.

- CIN 2/3 IS UNLIKELY TO DEVELOP DURING A 2 YEARS FOLLOW-UP IN WOMEN WHO TESTED NEGATIVE FOR HR-HPV BUT HAD LESION CYTOLOGICALLY IDENTIFIED AS ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE (ASCUS) BORDERLINE OR MILD DYSPLASIA.

- IN THESE WOMEN THE CYTOLOGIC RESULTS ARE LIKELY TO RETURN TO THE NORMAL.
- THOSE WHO TEST POSITIVE FOR LOW-RISK HPV RARELY BECOME PERSISTENT CARRIERS AND THE PROBABILITY OF THEIR LESIONS TO PROGRESS TO CIN 2/3 IS EXTREMELY LOW.

- THE RISK OF PROGRESSION (GIVEN PERSISTANCE) IS SIGNIFICANTLY HIGHER FOR CARRIERS OF HPV-16 AND HPV-18 COMPARED WITH CARRIERS OF ANY OF THE OTHER HIGH RISK TYPES.

RELEVANCE OF HPV-16 AND HPV-18 IN CERVICAL CANCER AND PRECANCEROUS LESIONS

- OF MORE THAN 35 TYPES OF HPV FOUND IN GENITAL TRACT, HPV-16 ACCOUNTS FOR 50 TO 60% OF ALL CERVICAL CANCER CASES IN MOST COUNTRIES FOLLOWED BY HPV-18 (10-20%), HPV-45 (4-8%) AND HPV-31(1- 5%).

- THE 5 MOST COMMON HPV TYPES (16,18,45,31,33) ARE FOUND IN 80% OF SQUAMOUS CELL CARCINOMA AND 94% OF ADENOCARCINOMA.
- IN MOST STUDIES, HPV-18 PREDOMINATES IN ADENOCARCINOMAS.

OTHER ENVIRONMENTAL RISK FACTORS FOR CERVICAL CANCER

- HPV IS A NECESSARY FACTOR FOR CERVICAL CANCER.
- THE NUMBER OF PARTNERS REFLECTS THE PROBABILITY OF HPV EXPOSURE.

LONG TERM USE OF ORAL CONTRACEPTIVES (OCs)

- WOMEN WHO EVER USED OCs HAVE A SIGNIFICANT INCREASED RISK OF CERVICAL CANCER.
- USE OF OCs FOR LESS THAN 5 YEARS WAS NOT RELATED TO CERVICAL CANCER.
- BUT THE RISK INCREASES SIGNIFICANTLY WITH THE USE OF OCs 5 TO 9 YEARS OR MORE.

- THE EVIDENCE OF ASSOCIATION BETWEEN CERVICAL CANCER AND THE USE OF OCs IS NOT CONSISTENT.

HIGH PARITY

- WOMEN WHO REPORTED 7 OR MORE FULL-TERM PREGNANCIES AND WERE HPV POSITIVE HAD A 4 FOLD INCREASE IN RISK OF CERVICAL CANCER COMPARED WITH NULLIPAROUS HPV POSITIVE WOMEN WITH SIMILAR CHARACTERISTICS.

- THE RISK FOR WOMEN WHO HAVE USED OCs LONGER THAN 5 YEARS AND HAD MORE THAN 5 FULL-TERM PREGNANCIES IS SIGNIFICANTLY INCREASED (11 FOLD).

CIGARETTE SMOKING

- CARCINOGENIC EFFECT OF CIGARETTE SMOKING IN WOMEN WITH PERSISTENT HPV INFECTION HAS BEEN PROVED.
- IARC MONOGRAPHIC PROGRAM REVIEWED THE EVIDENCE IN 2002, AND CONCLUDED THAT SMOKING WAS AN INDEPENDENT RISK FACTOR FOR CERVICAL CANCER.

- THE MECHANISM BY WHICH CIGARETTE SMOKING MAY AFFECT CERVICAL CANCER REMAINS ELUSIVE: DIRECT EFFECT OF TOBACCO METABOLITES, INDIRECT EFFECTS RELATED TO TOBACCO-INDUCED IMMUNODEPRESSION OR REDUCED INTAKE OF DIARY OXYDANTS.

HIV COINFECTION

- THE EVIDENCE OF A POSSIBLE INTERACTION BETWEEN HPV AND HIV AT THE ORIGIN OF CERVICAL CANCER WAS FORMALLY RECOGNIZED WHEN CERVICAL CANCER WAS INCLUDED AS ONE OF THE CRITERIA FOR AIDS. THE SUBSEQUENT LITERATURE LARGELY CONFIRMED THE EVIDENCE.

CONINFECTION WITH OTHER SEXUALLY TRANSMITTED INFECTIOUS AGENTS

- RESULTS FROM THE IARC MULTICENTER STUDY FOUND A 2-FOLD INCREASE IN RISK OF CERVICAL CANCER WHEN ANTIBODIES TO CHLAMYDIA TRACHOMATIS OR HSV WERE PRESENT.

METHODS FOR DETECTION OF HPV INFECTION AND ITS CLINICAL UTILITY

- HPVs CANNOT BE CULTURED AND THE DETECTION OF VIRUS RELIES ON VARIETY OF TECHNIQUES USED IN IMMUNOLOGY, SEROLOGY, AND MOLECULAR BIOLOGY.
- CURRENTLY THE ONLY FDA-APPROVED COMMERCIALLY AVAILABLE METHOD FOR THE DETECTION OF HPV DNA IS THE HYBRID CAPTURE ASSAY VERSION hc2 WHICH IS AVAILABLE TO DETECT 13 HIGH RISK TYPES OF HPV.

- THE ADVANTAGE OF PCR-BASED METHODS FOR THE DETECTION OF HPV DNA IS THAT THEY ALLOW FOR THE IDENTIFICATION OF DIFFERENT TYPES OF HPV.

CLINICAL UTILITY OF HPV TESTING

- THE FIRST ADVANTAGE IS THE HIGHER SENSIBILITY, AND A HIGH SENSIBILITY IS PARTICULARLY IMPORTANT IN SETTINGS WHERE WOMEN WILL BE SCREENED ONLY ONCE OR TWICE IN THEIR LIFETIMES.

- THE SECOND ADVANTAGE IS THAT HPV DNA TESTING NOT ONLY IDENTIFIES WOMEN WITH CERVICAL DISEASE BUT ALSO THOSE WHO ARE AT RISK FOR DEVELOPING CERVICAL NEOPLASIA WITHIN THE NEXT 3 TO 10 YEARS. THAT IS PARTICULARLY IMPORTANT FOR DEVELOPING COUNTRIES THAT MIGHT NOT HAVE SUFFICIENT RESOURCES TO SCREEN ALL WOMEN AT 5 TO 10 YEARS INTERVALS.

- THE INTERPRETATION OF THE TEST IS OBJECTIVE AND DOES NOT HAVE THE INHERENT SUBJECTIVITY OF VISUAL SCREENING METHODS OR CERVICAL CYTOLOGIC ASSESSMENT.

HPV DNA TESTING AS A PRIMARY SCREENING TEST

COUNTRY	N° OF STUDY PARTICIPANTS	SENSITIVITY OF CYTOLOGY	SENSITIVITY OF HPV DNA TESTING
MEXICO	6115	57	94
COSTA RICA	6176	80	86
SOUTH AFRICA	2925	74	84
GERMANY	8466	98	37

COUNTRY	N° OF STUDY PARTICIPANTS	SPECIFICITY CYTOLOGIC TESTING	SPECIFICITY HPV DNA TESTING
MEXICO	6115	99	94
COSTA RICA	6176	95	94
SOUTH AFRICA	2925	88	82
GERMANY	8466	95	99

HPV DNA TESTING FOR FOLLOW-UP POST TREATMENT

- TREATED WOMEN REMAIN AT INCREASED RISK FOR CERVICAL CANCER FOR AT LEAST 8 YEARS COMPARED WITH THE GENERAL FEMALE POPULATION.

- COMBINATION OF CYTOLOGIC AND COLPOSCOPIC ASSESSMENTS HAS BEEN USED TO FOLLOW UP WOMEN POST TREATMENT.
- SENSITIVITY, SPECIFICITY AND NPV OF HPV DNA TESTING OR THE POST-TREATMENT DETECTION OF CIN2/3 ARE 96.5%, 77.3%, 98.8% RESPECTIVELY.

- THE INFORMATION GATHERED SO FAR SUGGESTS THAT HPV TESTING MAY BE SIGNIFICANTLY MORE RELIABLE THAN COLPOSCOPY AND CYTOLOGY.

HPV VACCINES

- ONE VACCINE, A QUADRIVALENT VACCINE AGAINST HPV TYPES 6,11,16 AND 18 KNOWN AS GARADSIL (MERCK) WAS APPROVED BY THE FEDERAL DRUG ADMINISTRATION (FDA) FOR PREVENTION OF CERVICAL CANCER, CERVICAL CANCER PRECURSORS, VULVAR AND VAGINAL CANCER PRECURSORS ASSOCIATED WITH HPV 16 AND 18.

- THE MAIN VACCINES COMPONENTS ARE RECOMBINANT VIRAL CAPSID PROTEINS ASSEMBLED INTO VIRUS-LIKE PARTICLES AND ALUM-BASED ADJUVANTS.

- IF GIVEN BEFORE HPV INFECTION, THE VACCINES, WHICH INDUCE HPV TYPE-SPECIFIC, VIRUS-NEUTRALIZING ANTIBODIES, HAVE PROVEN TO BE BOTH SAFE AND HIGHLY EFFECTIVE AT PREVENTING HPV INFECTION AND ITS CLINICAL CONSEQUENCES, INCLUDING HIGH-GRADE CERVICAL LESIONS.

- BECAUSE THEY INCORPORATE ONLY 2 HPV TYPES MOST COMMONLY ASSOCIATED WITH CERVICAL CANCERS (HPV-16 AND HPV-18), THEY CAN ONLY PREVENT ABOUT 70% OF CERVICAL CANCERS.

- VACCINES TO TREAT EXISTING HPV INFECTION ARE UNDER DEVELOPMENT BUT ARE UNLIKELY TO BECOME CLINICALLY AVAILABLE IN THE NEAR FUTURE.

CONCLUSION

- ETIOLOGY STUDIES OF CERVICAL CANCER HAVE IDENTIFIED SEVERAL HPV TYPES AS NECESSARY FOR THE DEVELOPMENT OF CERVICAL CANCER. THESE FINDINGS RESULTED IN NOVEL SCREENING AND VACCINATION STRATEGIES FOR PREVENTION OF CERVICAL CANCER.