HPV Prevention and Control Board

Country meeting 'Prevention and control of HPV and HPV related cancers in Denmark: lessons learnt and the way forward'

17-18 November 2016

Copenhagen, Denmark

BACKGROUND DOCUMENT

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Content

Introduction

Objectives of the meeting:

1. Provide an overview of the health care systems and vaccination programs.
2. Review the epidemiological situation of HPV infection and related diseases.
3. Give an overview of the current prevention and control measures on HPV.
4. Discuss the challenges and the progress achieved in HPV prevention.
5. Review the possible implementation of new prevention strategies, control measures and monitoring systems.
6. Discuss the successes, issues and barriers to overcome, and the way forward.

Target audience:

- Projects and organisation representatives involved in HPV control and prevention
- Representatives of health organisations involved in the prevention and control of HPV and/or other health issues
- HPV prevention and control Board advisors

Purpose of the background document

This background document provides an overview of articles related to the meeting and a concise bibliography of speakers. The main purpose of the document is to frame the topics of the country meeting on 'Prevention and control of HPV and HPV related cancers in Denmark: lessons learnt and the way forward', 17-18 November 2016, Copenhagen.

The document should not be considered as an an exhaustive report of scientific articles related to the themes of the meeting.

Inclusion of references in this document does not indicate that the Executive Secretariat agrees with the content or correctness of the content. The first objective of this list is to give an overview of what has been published on this topic.

References applicable to different sessions are duplicated in all relevant sessions, abstract of the reference is only added the first time the reference is mentioned.

Part 1: Presentation related references by session

List obtained via speakers and via a PubMed search. The items retrieved via PubMed were added in Endnote (version X7.7.1). The background document contains a selected list of publications based on a manual selection in Endnote.

Session 2 The Danish Health Care System

The Danish health care system and overview of all vaccinations programs
Camilla Rosengaard Villumsen

References session 1 via PubMed search

A PubMed search was performed with the following selection criteria: 1) Denmark AND "Health Care System" in the last 10 years: 107 items retrieved in Endnote.

The list contains a manual selection of publications relevant to session 1.

Andersen, R. S., P. Vedsted, F. Olesen, F. Bro and J. Sondergaard (2011). "Does the organizational structure of health care systems influence care-seeking decisions? A qualitative analysis of Danish cancer patients' reflections on care-seeking." Scand J Prim Health Care **29**(3): 144-149.

OBJECTIVE: The absence of a more significant improvement in cancer survival in countries such as the UK and Denmark may be partly rooted in delayed care-seeking among cancer patients. Past research on patient delay has mainly focused on patient characteristics (e.g. sociodemographic and psychological factors and symptom recognition) as causes of delayed care-seeking, while few studies have examined how the organizational structure of health care systems may influence patients' reflections on seeking care. The aim of this study was to explore this relationship. DESIGN: The analysis presented is based on semi-structured interviews with 30 cancer patients and their families. RESULTS: The article raises two hypotheses on the relationship between structural elements of a health care system and people's reflections on seeking health care: (1) Gatekeeping introduces an asymmetrical relationship between the patient and the GP which potentially results in self-restricting care-seeking, (2) Continuity in the doctor-patient relationship may negatively influence patient reflections on access to health care, as the focus shifts from the medical issues of the consultation to reflections on how to properly interact with the GP and the system in which she/he is situated. CONCLUSION: It is concluded that these hypotheses form a sound basis for further primary care research on how the organizational structure of health care systems influences patient reflections on access to medical care.

Dalsted, R. J., A. D. Guassora and T. Thorsen (2011). "Danish general practitioners only play a minor role in the coordination of cancer treatment." Dan Med Bull **58**(1): A4222.

INTRODUCTION: Despite initiatives to integrate treatment and care across organisations, patient trajectories in Danish health-care are not well coordinated. Coordination among many health-care professionals is essential, and it is frequently suggested that a single person should perform the task of coordination. The aim of the article is to discuss whether general practitioners (GPs) may play a coordinating role for individual patients in Danish cancer treatment. MATERIAL AND METHODS: This study is based on individual interviews and focus groups analyzed by meaning condensation. RESULTS: The GP's potential to coordinate patient trajectories was limited by lack of involvement of the GPs by other health-care professionals and lack of needed information. Furthermore, many patients do not regard their GP as a coordinator. Patients who contacted their GP during treatment typically had a close relationship with their GP prior to their cancer diagnosis. In cases with a more distant relationship, patients did not see a need for the GP's involvement. The majority of patients' trajectories were decided within hospitals. The level of information provided to GPs varied much between hospitals and wards. In the majority of cases, GPs had no access to information or were not informed about hospital decisions affecting the patients' trajectories, and they were therefore unable to perform a coordinating role. CONCLUSION: GPs only

played a minor or no role at all as coordinators of individual cancer patient trajectories. The findings of the present study question the idea that coordination throughout the entire health-care system may be assigned to a single individual as the involved parties belong to different organizations with different goals, managements and economic resources.

Davidsen, A. S. (2010). "[Talking therapy as part of the general practitioner's normal working day]." Ugeskr Laeger **172**(27): 2025-2029.

INTRODUCTION: The vast majority of patients with mental disorders are treated in general practice. In Denmark, GPs have received a special payment for delivering >>talking therapy<< since 1995. However, it has not been described how this service should be used. Reports from the Danish Psychiatric Society and the Danish College of General Practitioners are paving the way for greater involvement of GPs in psychotherapy. The aim of the study was to investigate how GPs perceive that talking therapy could fit into their day-to-day efforts in the clinic. MATERIAL AND METHODS: This is a qualitative study which is based on interviews with Danish GPs. The analysis was based on interpretative phenomenological analysis. RESULTS: GPs organized talking therapy very differently and offered it to different extents. The context and conditions differed greatly from those of the secondary health care system, as the treatment was always an extension of a pre-existing doctor-patient relationship. Therapy was only offered if the communication between GP and patient was good beforehand. Talking therapy would not be delivered if the GPs' time conditions did not allow this, and when time was insufficient it was always the emotional area that was forfeited. CONCLUSION: The introduction of a psychological thinking to the standardised theoretical curriculum of general practice should be considered. There is a need for research into talking therapy and quality-assured training and supervision of GPs.

Jensen, H. I., M. Christensen, M. D. Hansen, S. J. Jorgensen, A. L. Sorensen and J. Mainz (2010). "[Patient safety in a health technology assessment perspective]." Ugeskr Laeger **172**(21): 1606-1609.

The Danish Act of Patient Safety entered into force in 2004. This paper studies the consequences of the Act for the health care system and its users by a literature evaluation and an interview study with key persons. Despite the substantial resources spent on the reporting system, no evidence is found that the Act has an improved effect on patient safety. One of the biggest barriers for reporting adverse events is a lack of follow-up and feedback. Research into the patient's role on preventing adverse events is limited. The possibilities created by the Act should be utilized to their full potential.

Jensen, L. F., T. O. Mukai, B. Andersen and P. Vedsted (2012). "The association between general practitioners' attitudes towards breast cancer screening and women's screening participation." BMC Cancer **12**: 254.

BACKGROUND: Breast cancer screening in Denmark is organised by the health services in the five regions. Although general practitioners (GPs) are not directly involved in the screening process, they are often the first point of contact to the health care system and thus play an important advisory role. No previous studies, in a health care setting like the Danish system, have investigated the association between GPs' attitudes towards breast cancer screening and women's participation in the screening programme. METHODS: Data on women's screening participation was obtained from the regional screening authorities. Data on GPs' attitudes towards breast cancer screening was taken from a previous survey among GPs in the Central Denmark Region. This study included women aged 50-69 years who were registered with a singlehanded GP who had participated in the survey. RESULTS: The survey involved 67 singlehanded GPs with a total of 13,288 women on their lists. Five GPs (7%) had a negative attitude towards breast cancer screening. Among registered women, 81% participated in the first screening round. Multivariate analyses revealed that women registered with a GP with a negative attitude towards breast cancer screening were 17% (95% CI: 2-34%) more likely to be non-participants compared with women

registered with a GP with a positive attitude towards breast cancer screening. CONCLUSION: The GPs' attitudes may influence the participation rate even in a system where GPs are not directly involved in the screening process. However, further studies are needed to investigate this association.

Jensen, N. K., M. Norredam, T. Draebel, M. Bogic, S. Priebe and A. Krasnik (2011). "Providing medical care for undocumented migrants in Denmark: what are the challenges for health professionals?" BMC Health Serv Res **11**: 154.

BACKGROUND: The rights of undocumented migrants are frequently overlooked. Denmark has ratified several international conventions recognizing the right to health care for all human beings, but has very scanty legislation and no existing policies for providing health care to undocumented migrants. This study focuses on how health professionals navigate and how they experience providing treatment for undocumented migrants in the Danish health care system. METHODS: The study was carried out as part of an EU-project on European Best Practices in Access, Quality and Appropriateness of Health Services for Immigrants in Europe (EUGATE). This presentation is based on 12 semi-structured interviews with general practitioners (9) and emergency room physicians (3) in Denmark. RESULTS: The emergency room physicians express that treatment of undocumented migrants is no different from the treatment of any other person. However, care may become more complicated due to lack of previous medical records and contact persons. Contrary to this, general practitioners explain that undocumented migrants will encounter formal barriers when trying to obtain treatment. Additional problems in the treatment of undocumented migrants include language issues, financial aspects for general practitioners, concerns about how to handle the situation including possibilities of further referrals, and an uncertainty as to whether to involve the police. CONCLUSIONS: The health professionals in our study describe that undocumented migrants experience an unequal access to primary care facilities and that great uncertainties exist amongst health professionals as how to respond in such situations. The lack of official policies concerning the right to health care for undocumented migrants continue to pass on the responsibility to health professionals and, thereby, leaves it up to the individual to decide whether treatment can be obtained or not.

Johannesdottir, S. A., E. Horvath-Puho, V. Ehrenstein, M. Schmidt, L. Pedersen and H. T. Sorensen (2012). "Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions." Clin Epidemiol **4**: 303-313.

The Danish health care system provides partial reimbursement of most prescription medications in Denmark. The dispensation of prescription medications is registered in administrative databases. Each time a prescription is redeemed at a pharmacy, an electronic record is generated with information related to the user, prescriber, the pharmacy, and the dispensed drug. The National Health Service gathers this information for administration of the drug reimbursement plan. Recently, this information became the basis for the establishment of a new research database, the Danish National Database of Reimbursed Prescriptions (DNDRP). In this paper, we review the content, coverage, quality, linkage, access, and research possibilities of this new database. The database encompasses the reimbursement records of all reimbursed drugs sold in community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004. On average, approximately 3.5 million users are recorded in the database each year. During the coverage period, the number of annual prescription redemptions increased by 15%. Most dispensed prescriptions are in the categories "alimentary tract and metabolism", "cardiovascular system", "nervous system", and "respiratory system". Individuals are identified by the unique central personal registration (CPR) number assigned to all persons born in or immigrating to Denmark. The new database fully complies with Denmark's Act on Processing of Personal Data, while avoiding additional restrictions imposed on data use at the Danish National Prescription Registry, administered by Statistics Denmark. Most importantly, CPR numbers are reversibly encrypted, which allows re-identification of drug users; furthermore, the data

access is possible outside the servers of Statistics Denmark. These features open additional opportunities for international collaboration, validation studies, studies on adverse drug effects requiring review of medical records, studies involving contact to general practitioners, and linkage of prescription data to other clinical and research databases. The DNDRP thus is a valuable data source for pharmacoepidemiological research.

Kjaer, N. K., T. Kodal and D. Qvesel (2010). "The role of general practice in postgraduate basic training." Med Teach **32**(10): e448-452.

BACKGROUND: In recent years, there has been growing interest in the role of primary care in postgraduate training. Relatively little has been published about benefits of early and sustained postgraduate basic training in general practice, especially for doctors with other ambitions than family medicine. AIM: To explore young Danish doctors' views on basic medical training including views on the participation of general practice. METHODS: We conducted a cross-sectional survey of all Danish doctors, who took part in the postgraduate basic training programmes in 2009. The survey consisted of rating scale and qualitative questions. We used a phenomenological approach. RESULTS: Almost all of the young Danish doctors responding felt that training in general practice is a necessary part of a postgraduate basic training programme. Early training in primary care not only gives doctors a broad understanding of the health care system but also strengthens the ability to collaborate with general practitioners upon entering another specialty. It also develops important medical and communicative competences. The training in general practice is considered beneficial for the development of professional identity. The educational environment in general practice is rated highly. CONCLUSION: The inclusion of family medicine in postgraduate basic training should be considered for all doctors.

Lundstrom, L. H., A. T. Johnsen, L. Ross, M. A. Petersen and M. Groenvold (2011). "Cross-sectorial cooperation and supportive care in general practice: cancer patients' experiences." Fam Pract **28**(5): 532-540.

BACKGROUND: Cancer care usually involves several health professionals from different parts of the health care system. Often, the GP has an important role. Patients' experiences of continuity and support may be related to characteristics of health care, disease or patients. OBJECTIVES: To investigate Danish cancer patients' experiences of their contact to the GP and the cooperation between the GP and the hospital. METHODS: A national cross-sectional questionnaire study in three representative counties of Denmark. Based on a review of medical records from all hospital departments treating cancer patients, a random sample of 1490 patients completed a validated questionnaire regarding patient experiences. A mixed methods approach was applied. Associations between patient experiences and background variables were analysed in ordinal logistic regression models and patients' written comments were analysed qualitatively. RESULTS: One-third of the patients evaluated the cooperation between hospitals and primary care as suboptimal. Younger patients and patients from the capital Copenhagen were most dissatisfied. A third had needed support from their GP, and 41% of these patients had not fully received what they needed. Older patients, patients in Stage 1 and patients from surgical departments were least likely to have needed their GP's support. Patients described support from the GP as empathic behaviour and help with coordinating health services. CONCLUSIONS: A substantial number of cancer patients experienced suboptimal cross-sectorial cooperation and supportive care. Efforts to improve cancer care cooperation may focus on the possible supportive role of the GP as it seems that there is an untapped potential in primary care.

Mainz, J., S. Kristensen and P. Bartels (2015). "Quality improvement and accountability in the Danish health care system." Int J Qual Health Care **27**(6): 523-527.

Denmark has unique opportunities for quality measurement and benchmarking since Denmark has well-developed health registries and unique patient identifier that allow all registries to include patient-level data and combine data into sophisticated quality performance monitoring. Over decades, Denmark has developed and implemented national quality and patient safety initiatives in the healthcare system in terms of national clinical guidelines, performance and outcome measurement integrated in clinical databases for important diseases and clinical conditions, measurement of patient experiences, reporting of adverse events, national handling of patient complaints, national accreditation and public disclosure of all data on the quality of care. Over the years, Denmark has worked up a progressive and transparent just culture in quality management; the different actors at the different levels of the healthcare system are mutually attentive and responsive in a coordinated effort for quality of the healthcare services. At national, regional, local and hospital level, it is mandatory to participate in the quality initiatives and to use data and results for quality management, quality improvement, transparency in health care and accountability. To further develop the Danish governance model, it is important to expand the model to the primary care sector. Furthermore, a national quality health programme 2015-18 recently launched by the government supports a new development in health care focusing upon delivering high-quality health care-high quality is defined by results of value to the patients.

Olejaz, M., A. Juul Nielsen, A. Rudkjobing, H. Okkels Birk, A. Krasnik and C. Hernandez-Quevedo (2012). "Denmark health system review." Health Syst Transit **14**(2): i-xxii, 1-192.

Denmark has a tradition of a decentralized health system. However, during recent years, reforms and policy initiatives have gradually centralized the health system in different ways. The structural reform of 2007 merged the old counties into fewer bigger regions, and the old municipalities likewise. The hospital structure is undergoing similar reforms, with fewer, bigger and more specialized hospitals. Furthermore, a more centralized approach to planning and regulation has been taking place over recent years. This is evident in the new national planning of medical specialties as well as the establishment of a nationwide accreditation system, the Danish Healthcare Quality Programme, which sets national standards for health system providers in Denmark. Efforts have also been made to ensure coherent patient pathways - at the moment for cancer and heart disease - that are similar nationwide. These efforts also aim at improving intersectoral cooperation. Financially, recent years have seen the introduction of a higher degree of activity-based financing in the public health sector, combined with the traditional global budgeting.A number of challenges remain in the Danish health care system. The consequences of the recent reforms and centralization initiatives are yet to be fully evaluated. Before this happens, a full overview of what future reforms should target is not possible. Denmark continues to lag behind the other Nordic countries in regards to some health indicators, such as life expectancy. A number of risk factors may be the cause of this: alcohol intake and obesity continue to be problems, whereas smoking habits are improving. The level of socioeconomic inequalities in health also continues to be a challenge. The organization of the Danish health care system will have to take a number of challenges into account in the future. These include changes in disease patterns, with an ageing population with chronic and long-term diseases; ensuring sufficient staffing; and deciding how to improve public health initiatives that target prevention of diseases and favour health improvements.

Pedersen, K. M., J. S. Andersen and J. Sondergaard (2012). "General practice and primary health care in Denmark." J Am Board Fam Med **25 Suppl 1**: S34-38.

General practice is the corner stone of Danish primary health care. General practitioners (GPs) are similar to family physicians in the United States. On average, all Danes have 6.9 contacts per year with their GP (in-person, telephone, or E-mail consultation). General practice is characterized by 5 key components: (1) a list system, with an average of close to 1600 persons on the list of a typical GP; (2) the GP as gatekeeper and first-line provider in the sense that a referral from a GP is required for most office-

based specialists and always for in- and outpatient hospital treatment; (3) an after-hours system staffed by GPs on a rota basis; (4) a mixed capitation and fee-for-service system; and (5) GPs are self-employed, working on contract for the public funder based on a national agreement that details not only services and reimbursement but also opening hours and required postgraduate education. The contract is (re)negotiated every 2 years. General practice is embedded in a universal tax-funded health care system in which GP and hospital services are free at the point of use. The current system has evolved over the past century and has shown an ability to adapt flexibly to new challenges. Practice units are fairly small: close to 2 GPs per unit plus nurses and secretaries. The units are fully computerized, that is, with computer-based patient records and submission of prescriptions digitally to pharmacies etc. Over the past few years a decrease in solo practices has been seen and is expected to accelerate, in part because of the GP age structure, with many GPs retiring and new GPs not wanting to practice alone. This latter workforce trend is pointing toward a new model with employed GPs, particularly in rural areas.

Salomonsen, L. J., L. Skovgaard, S. la Cour, L. Nyborg, L. Launso and V. Fonnebo (2011). "Use of complementary and alternative medicine at Norwegian and Danish hospitals." BMC Complement Altern Med **11**: 4.

BACKGROUND: Several studies have found that a high proportion of the population in western countries use complementary and alternative medicine (CAM). However, little is known about whether CAM is offered in hospitals. The aim of this study was to describe to what extent CAM is offered in Norwegian and Danish hospitals and investigate possible changes in Norway since 2001. METHODS: A one-page questionnaire was sent to all included hospitals in both countries. The questionnaire was sent to the person responsible for the clinical activity, typically the medical director. 99 hospitals in the authority (85%) in Norway and 126 in Denmark (97%) responded. Given contact persons were interviewed. RESULTS: CAM is presently offered in about 50% of Norwegian hospitals and one-third of Danish hospitals. In Norway CAM was offered in 50 hospitals, 40 of which involved acupuncture. 19 hospitals gave other alternative therapies like biofeedback, hypnosis, cupping, ear-acupuncture, herbal medicine, art therapy, homeopathy, reflexology, thought field therapy, gestalt therapy, aromatherapy, tai chi, acupressure, yoga, pilates and other. 9 hospitals offered more than one therapy form. In Denmark 38 hospitals offered acupuncture and one Eye Movement Desensitization and Reprocessing Light Therapy. The most commonly reported reason for offering CAM was scientific evidence in Denmark. In Norway it was the interest of a hospital employee, except for acupuncture where the introduction is more often initiated by the leadership and is more based on scientific evidence of effect. All persons (except one) responsible for the alternative treatment had a medical or allied health professional background and their education/training in CAM treatment varied substantially. CONCLUSIONS: The extent of CAM being offered has increased substantially in Norway during the first decade of the 21(st) century. This might indicate a shift in attitude regarding CAM within the conventional health care system.

Sogaard, R., M. S. Pedersen and M. Bech (2013). "To what extent does employer-paid health insurance reduce the use of public hospitals?" Health Policy **113**(1-2): 61-68.

OBJECTIVE: This study examines the extent to which employer-paid health insurance has led to substitution of public with private hospital use in Denmark. METHODS: Individual-person-level data for the entire Danish privately employed, full-time working population is used in an observational design. The effect of having employer-paid health insurance on the utilisation of public hospitals is estimated using propensity score matching in order to control for risk selection, based on a number of individual- and company-level characteristics. The outcome is defined as the total consumption of health care services provided by public hospitals. RESULTS: The effect of employer-paid health insurance is estimated to correspond to a significant 10% reduction in the total use of public hospitals. The effect appears to be robust to alternative methodological specifications and is supported from the analysis of alternative

outcome measures. CONCLUSION: The rise in the number of individuals with employer-paid health insurance seems to have alleviated the pressure on public hospitals in Denmark. Future studies should confirm the magnitude of this effect, preferably based on empirical data with repeated measurements of insurance status.

Vandborg, M. P., R. D. Christensen, J. Kragstrup, K. Edwards, P. Vedsted, D. G. Hansen and O. Mogensen (2011). "Reasons for diagnostic delay in gynecological malignancies." Int J Gynecol Cancer **21**(6): 967-974.

INTRODUCTION: To describe the different delay types in women with gynecological cancer and to analyze the relationship between diagnostic delay and a number of characteristics for patients, cancers, and the health care system. METHOD: Data were obtained from 4 different questionnaires, the Electronic Patient Journal (EPJ), and the Danish Gynecological Cancer Database (DGCD). A total of 161 women with ovarian cancer (63), endometrial cancer (50), cervical cancer (34), and vulvar cancer (14) were included. Outcome measures were different delay types counted in days and 4 clinically important variables' impact on the diagnostic delay: presence of alarm symptoms, age (divided into 2 groups: </=60 or >60 years), performance of gynecological examination by the general practitioner (GP), and notification of cancer suspicion on first referral from GP. RESULTS: Across cancer types, median total delay was 101 days. Some 10% of women experienced the longest delay with a total delay of 436 days or more. Vulva cancer had the longest delay, whereas women with ovarian cancer had the shortest delay. More than one third (39%) of the women consulted their GP for reasons other than the predefined alarm symptoms. Gynecological examination by the GP was less likely to be performed if the woman did not present with vaginal bleeding. The length of the delay was shortened by performance of a gynecological examination by the GP and a primary referral from the GP raising the receiver's suspicion of cancer. CONCLUSION: Reducing diagnostic delays should be achievable, particularly for those most delayed, and interventions aimed at reducing delays need to be developed. Creation of new valid instruments for measuring delay is essential in future research.

Vedsted, P., R. P. Hansen and F. Bro (2011). "[General practice and early cancer diagnosis]." Ugeskr Laeger **173**(24): 1712-1715.

About 85% of cancer patients present with symptoms to general practice. The health care system should be organised in a way that GPs are able to refer patients to timely and early cancer diagnosis. The GP works in an area where symptoms most often are benign and cancer is rare. Only a minority of the symptoms in the population are presented to the GP. The GP must refer many of these knowing that generally the positive predictive value is 2-10%. To be able to ensure the best primary cancer diagnostic pathway we need much more research on symptoms, use of diagnostics and the way to organise this in a health care system where every third citizen will get cancer.

Viskum, B., A. G. Juhl, I. Pedersen and M. D. Staehr (2011). "[Need for innovation in working with adverse events]." Ugeskr Laeger **173**(41): 2554-2556.

Patient safety has been in focus in the Danish health care for the past five years, with a mandatory reporting system for adverse events/incidents at hospitals. The incidents have been analysed with the Root Cause Analysis. This analysis is a relatively simple linear cause effect analysis, however, not suitable for the use in a complex sociotechnic health-care system. There is a need for other methods and approaches, which can reflect this complexity and focus on the future prospective prevention.

Session 3 Epidemiology, burden of disease and surveillance

Epidemiology of HPV and burden of HPV-related neoplasia in Denmark.
Susanne Krüger Kjær
References provided by the speaker:

Kjaer, S. K., C. Munk, J. Junge and T. Iftner (2014). "Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention?" Cancer Causes Control **25**(2): 179-189.

BACKGROUND: Assessment of the prevaccination type-specific prevalence of human papillomavirus (HPV) in the general population is important for the prediction of the impact of HPV vaccination. METHODS: We collected consecutively residual specimens from liquid-based cytology samples from 40,382 women from the general population in Copenhagen, Denmark, during 2002-2005. All samples were tested for high-risk HPV using the Hybrid Capture 2 technique, and genotyping was done using LiPa (Innogenetics). Through linkage with the Pathology Data Bank, we obtained information on the cytology result, and histology if any, on all women. RESULTS: The participants were 14-95 years of age (median age 37 years) at enrollment. The overall prevalence of HR HPV was 20.6 % ranging from 46.0 % in 20-23-year-old women to 5.7 % in women 65 years or older. Independently of cytology/histology, HPV16 was the most prevalent type. For virtually all HPV types, the occurrence of CIN3+ was higher when the specific HPV type was present together with HPV16 than it was together with other high-risk HPV types than HPV16 or if the HPV type occurred as a single infection. The prevalence of HPV16 and/or HPV18 was 74 % in cervical cancer and the corresponding prevalence of HPV16/18/31/33/45/52/58 was 89 %. CONCLUSION: This study forms a valuable starting point for monitoring the effect of HPV vaccination in Denmark. In addition, the particular carcinogenic role of HPV16 and 18 is confirmed and may support a role of genotyping for HPV16 and 18 in cervical cancer screening.

Svahn, M. F., C. Munk, C. von Buchwald, K. Frederiksen and S. K. Kjaer (2016). "Burden and incidence of human papillomavirus-associated cancers and precancerous lesions in Denmark." Scand J Public Health **44**(6): 551-559.

AIM: The aim of the study was to investigate the incidence of human papillomavirus (HPV)-associated cancers in Denmark between 1978 and 2011, estimate the current absolute annual number (burden) of HPV-associated cancers (HPVaCa) and their precancerous lesions, and assess whether there is socioeconomic inequality in the risk of HPV-associated cancers. METHODS: From four nationwide population-based registries, information was collected on HPVaCa diagnosed during 1978-2011 and age-standardised incidence rate for each site by calendar year and birth cohort was calculated. Furthermore, the current annual burden of HPVaCa and severe precancerous lesions was estimated. Incidence rate ratios and corresponding 95% confidence intervals for HPVaCa were calculated according to socioeconomic status. RESULTS: The age-standardised incidence rate of HPV-associated cancers for the two sexes converged during the study period, and almost identical incidence rates were seen for women and men in the youngest birth cohorts. The current burden of HPV-associated lesions amounted to more than 5000 cases, the vast majority (85%) being severe precancerous lesions. The highest risk for HPV-associated cancers was associated with lower socioeconomic status. CONCLUSIONS THE BURDEN OF HPV-ASSOCIATED CANCERS AMONG MEN WILL LIKELY SURPASS THAT AMONG WOMEN IN THE NEAR FUTURE IF THE INCIDENCE TRENDS CONTINUE AS MANY OF THESE CANCERS AND THEIR PRECANCEROUS LESIONS ARE ASSOCIATED WITH HPV TYPE 16, A SUBSTANTIAL PROPORTION OF CASES ARE, IN THEORY, PREVENTABLE BY THE CURRENTLY AVAILABLE VACCINES.

Kjaer, S. K., K. Frederiksen, C. Munk and T. Iftner (2010). "Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence." J Natl Cancer Inst **102**(19): 1478-1488.

BACKGROUND: Infection with high-risk human papillomavirus (HPV) is the main cause of high-grade cervical intraepithelial neoplasia (CIN) and cancer. It has been suggested that information about high-risk HPV type-specific infection might make cervical cancer screening more effective. Persistent HPV infection could also be a useful screening marker. We estimated the long-term risk of high-grade CIN after one-time detection of high-risk HPV DNA and after persistent infection with individual high-risk HPV types. METHODS: A cohort of 8656 women from the general population of Denmark was examined twice, 2 years apart (first study examination: May 15, 1991, to January 31, 1993; second study examination: October 1, 1993, to January 31, 1995). The women underwent a gynecological examination and cervical cytology and had swabs taken for HPV DNA analysis by the Hybrid Capture 2 and line probe assays. The women were followed up through the nationwide Danish Pathology Data Bank for cervical neoplasia for up to 13.4 years. The absolute risk of developing cervical lesions before a given time was estimated as a function of time. RESULTS: For women with normal cytological findings who were concurrently HPV16 DNA positive at the second examination, the estimated probability of developing CIN grade 3 (CIN3) or worse within 12 years of follow-up was 26.7% (95% confidence interval [CI] = 21.1% to 31.8%). The corresponding risks among those infected with HPV18 was 19.1% (95% CI = 10.4% to 27.3%), with HPV31 was 14.3% (95% CI = 9.1% to 19.4%), and with HPV33 was 14.9% (95% CI = 7.9% to 21.1%). The absolute risk of CIN3 or worse after infection with high-risk HPV types other than HPV16, HPV18, HPV31, or HPV33 was 6.0% (95% CI = 3.8% to 8.3%). The estimated absolute risk for CIN3 or cancer within 12 years of the second examination among women who were HPV16 DNA positive at both examinations was 47.4% (95% CI = 34.9% to 57.5%); by contrast, the risk of CIN3 or worse following a negative Hybrid Capture 2 test was 3.0% (95% CI = 2.5% to 3.5%). CONCLUSION: HPV16, HPV18, HPV31, and HPV33 infection and especially HPV16 persistence were associated with high absolute risks for progression to high-grade cervical lesions. The results indicate the potential value of genotyping in cervical cancer screening. Given that HPV DNA-negative women retained their low risk of CIN3 or worse for many years, frequent screening of these women may be unnecessary.

HPV surveillance
Christian Munk
References provided by the speaker:

Nygard, M., B. T. Hansen, J. Dillner, C. Munk, K. Oddsson, L. Tryggvadottir, M. Hortlund, K. L. Liaw, E. J. Dasbach and S. K. Kjaer (2014). "Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance." PLoS One **9**(2): e88323.

BACKGROUND: Infection with high-risk human papillomavirus (HPV) is causally related to cervical, vulvar and vaginal pre-invasive neoplasias and cancers. Highly effective vaccines against HPV types 16/18 have been available since 2006, and are currently used in many countries in combination with cervical cancer screening to control the burden of cervical cancer. We estimated the overall and age-specific incidence rate (IR) of cervical, vulvar and vaginal cancer and pre-invasive neoplasia in Denmark, Iceland, Norway and Sweden in 2004-2006, prior to the availability of HPV vaccines, in order to establish a baseline for surveillance. We also estimated the population attributable fraction to determine roughly the expected effect of HPV16/18 vaccination on the incidence of these diseases. METHODS: Information on incident cervical, vulvar and vaginal cancers and high-grade pre-invasive neoplasias was obtained from high-quality national population-based registries. A literature review was conducted to define the fraction

of these lesions attributable to HPV16/18, i.e., those that could be prevented by HPV vaccination. RESULTS: Among the four countries, the age-standardised IR/10(5) of cervical, vaginal and vulvar cancer ranged from 8.4-13.8, 1.3-3.1 and 0.2-0.6, respectively. The risk for cervical cancer was highest in women aged 30-39, while vulvar and vaginal cancers were most common in women aged 70+. Age-standardised IR/10(5) of cervical, vulvar and vaginal pre-invasive neoplasia ranged between 138.8-183.2, 2.5-8.8 and 0.5-1.3, respectively. Women aged 20-29 had the highest risk for cervical pre-invasive neoplasia, while vulvar and vaginal pre-invasive neoplasia peaked in women aged 40-49 and 60-69, respectively. Over 50% of the observed 47,820 incident invasive and pre-invasive cancer cases in 2004-2006 can be attributed to HPV16/18. CONCLUSION: In the four countries, vaccination against HPV 16/18 could prevent approximately 8500 cases of gynecological cancer and pre-cancer annually. Population-based cancer and vaccination registries are essential to assess the predicted public health effects of HPV vaccination.

Nygard, M., A. Saah, C. Munk, L. Tryggvadottir, E. Enerly, M. Hortlund, L. G. Sigurdardottir, S. Vuocolo, S. K. Kjaer and J. Dillner (2015). "Evaluation of the Long-Term Anti-Human Papillomavirus 6 (HPV6), 11, 16, and 18 Immune Responses Generated by the Quadrivalent HPV Vaccine." Clin Vaccine Immunol **22**(8): 943-948.

This quadrivalent human papillomavirus (qHPV) (HPV6, -11, -16, and -18) vaccine long-term follow-up (LTFU) study is an ongoing extension of a pivotal clinical study (FUTURE II) taking place in the Nordic region. The LTFU study was designed to evaluate the effectiveness, immunogenicity, and safety of the qHPV vaccine (Gardasil) for at least 10 years following completion of the base study. The current report presents immunogenicity data from testing samples of the year 5 LTFU visit (approximately 9 years after vaccination). FUTURE II vaccination arm subjects, who consented to being followed in the LTFU, donated serum at regular intervals and in 2012. Anti-HPV6, -11, -16, and -18 antibodies were detected by the competitive Luminex immunoassay (cLIA), and in addition, serum samples from 2012 were analyzed by the total IgG Luminex immunoassay (LIA) (n = 1,598). cLIA geometric mean titers (GMTs) remained between 70% and 93% of their month 48 value depending on HPV type. For all HPV types, the lower bound of the 95% confidence interval (CI) for the year 9 GMTs remained above the serostatus cutoff value. The proportion of subjects who remained seropositive based on the IgG LIA was higher than the proportion based on cLIA, especially for anti-HPV18. As expected, the anti-HPV serum IgG and cLIA responses were strongly correlated for all HPV types. Anti-HPV GMTs and the proportion of vaccinated individuals who are seropositive remain high for up to 9 years of follow-up after vaccination.

Hansen, B. T., S. K. Kjaer, L. Arnheim-Dahlstrom, K. L. Liaw, K. E. Jensen, L. T. Thomsen, C. Munk and M. Nygard (2014). "Human papillomavirus (HPV) vaccination and subsequent sexual behaviour: evidence from a large survey of Nordic women." Vaccine **32**(39): 4945-4953.

OBJECTIVE: To assess whether recipients and non-recipients of the human papillomavirus (HPV) vaccine subsequently differ in terms of sexual risk taking behaviour. DESIGN: Cross-sectional survey. Sequential analyses constructed from self-reported age at vaccination, age at first intercourse and age at response. SETTING: A random selection of women aged 18-46 years living in Denmark, Norway and Sweden in 2011-2012, eligible for opportunistic or organized catch-up HPV vaccination. PARTICIPANTS: A total of 3805 women reported to have received the HPV vaccine and 40,247 reported not to have received it. Among vaccinees, 1539 received the HPV vaccine before or at the same age as sexual debut, of which 476 and 1063 were eligible for organized catch-up and opportunistic vaccination, respectively. MAIN OUTCOME MEASURES: Self-reported sexual behaviour, compared by hazard ratios and odds ratios for women who received the HPV vaccine before or at the same age as sexual debut versus women who did not receive the HPV vaccine. RESULTS: HPV vaccination did not result in younger age at first intercourse. Women who received the HPV vaccine before or at the same age as sexual debut did not have more sexual partners than did non-vaccinees. Non-use of contraception during first intercourse was more common

among non-vaccinees than among HPV vaccinees. The results were similar for organized catch-up and opportunistic vaccinees. CONCLUSION: Women who received the HPV vaccine before or at the same age as sexual debut did not subsequently engage more in sexual risk taking behaviour than women who did not receive the HPV vaccine.

Thomsen, L. T., M. Nygard, S. Stensen, B. Terning Hansen, L. Arnheim Dahlstrom, K. L. Liaw, C. Munk and S. K. Kjaer (2016). "Awareness of human papillomavirus after introduction of HPV vaccination: a large population-based survey of Scandinavian women." Eur J Cancer Prev.

Using a large, population-based survey, we assessed the levels and correlates of human papillomavirus (HPV) awareness among Scandinavian women after introduction of HPV vaccination. In 2011-2012, a random sample of women aged between 18 and 45 years from Denmark, Sweden and Norway received a questionnaire on lifestyle, health and HPV awareness. We included 47 895 women (response rate 60.6%) in our study. Country-specific and age-specific proportions of women who had heard of HPV in 2011-2012 (postvaccination survey) were compared with corresponding proportions in an identical survey from 2004-2005 (prevaccination survey, n=54 079, response rate 71.3%). Correlates of HPV awareness in the postvaccination survey were assessed by logistic regression. In all countries and age groups, awareness of HPV increased from the prevaccination to the postvaccination survey. In the postvaccination survey, HPV awareness was higher in Denmark (75.8%) and Sweden (74.8%) compared with Norway (62.4%), with greatest discrepancy among women aged between 18 and 19 years (Denmark: 74.9%, Sweden: 70.4%, Norway: 39.6%). Variables associated with low HPV awareness included the following: low education [</=12 vs. >16 years of schooling: odds ratio (OR)=0.45, 95% confidence interval (CI): 0.42-0.48], being a virgin (vs. nonvirgins: OR=0.74, 95% CI: 0.66-0.83), never having used condoms (vs. ever: OR=0.62, 95% CI: 0.56-0.67), nonuse of contraception at first intercourse (vs. use: OR=0.83, 95% CI: 0.79-0.88) and daily smoking (vs. never: OR=0.86, 95% CI: 0.80-0.92). HPV awareness in Scandinavia has increased since the introduction of HPV vaccination. However, 24-38% of Scandinavian women still have never heard of HPV. Future information efforts should target groups with low HPV awareness.

Baldur-Felskov, B., C. Dehlendorff, C. Munk and S. K. Kjaer (2014). "Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women." J Natl Cancer Inst **106**(3): djt460.

BACKGROUND: In clinical trials, vaccines against human papillomavirus (HPV) have been highly effective against HPV16- or HPV18-associated cervical lesions. The quadrivalent HPV vaccine was licensed in 2006 and subsequently implemented in the Danish vaccination program. The study aim was to use individual information on HPV vaccination status to assess subsequent risk of cervical lesions. METHODS: Using a cohort study design, we identified all girls and women born in Denmark in the period from 1989 to 1999 and obtained information on individual HPV vaccination status in the period from 2006 to 2012 from nationwide registries. Incident cases of cervical lesions were identified by linkage to the nationwide Pathology Data Bank. We compared vaccinated and unvaccinated girls and women stratified by birth cohort in Cox proportional hazards models. RESULTS: Risk of atypia or worse (atypia+) and of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) were statistically significantly reduced among vaccinated women in birth cohorts 1991 to 1994 (1991-1992atypia+: hazard ratio [HR] = 0.46, two-sided 95% confidence interval [CI] = 0.39 to 0.56; 1991-1992CIN2/3: HR = 0.56, 95% CI = 0.37 to 0.84; 1993-1994atypia+: HR = 0.40, 95% CI = 0.29 to 0.56; 1993-1994 CIN2/3: HR = 0.27, 95% CI = 0.10 to 0.67). The birth cohort 1989 to 1990 had a statistically significantly reduced risk of atypia+ (HR = 0.75; 95% CI = 0.65 to 0.86); the risk of CIN2/3 was also decreased but not statistically significant. No events occurred among girls in the birth cohort 1997 to 1999, whereas for the birth cohort 1995 to 1996 a hazard ratio could be calculated only for atypia+. CONCLUSIONS: Six years after licensure of the quadrivalent HPV vaccine in Denmark, a reduced risk of cervical lesions is observed at the population level.

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References session 3 via PubMed search

A PubMed search was performed with the following selection criteria: 1) Denmark AND HPV AND epidemiology; Denmark AND HPV AND burden of disease; Denmark AND HPV AND surveillance in the last 10 years: 266 items retrieved in Endnote. After removal of duplicates 133 references were withheld. 2) Denmark AND HPV AND side effects/adverse events in the last 10 years: 2 items were retrieved in Endnote.

The list contains a manual selection of publications relevant to session 3.

Andersen, A. S., A. S. Koldjaer Solling, T. Ovesen and M. Rusan (2014). "The interplay between HPV and host immunity in head and neck squamous cell carcinoma." Int J Cancer **134**(12): 2755-2763.

Persistent infection with human papillomavirus (HPV) type 16 is a major risk factor for the development of head and neck squamous cell carcinoma (HNSCC), in particular oropharyngeal squamous cell carcinoma (OPSCC). The oropharyngeal epithelium differs from the mucosal epithelium at other commonly HPV16-infected sites (i.e., cervix and anogenital region) in that it is juxtaposed with the underlying lymphatic tissue, serving a key immunologic function in the surveillance of inhaled and ingested pathogens. Therefore, the natural history of infection and immune response to HPV at this site may differ from that at other anatomic locations. This review summarizes the literature concerning the adaptive immune response against HPV in the context of HNSCC, with a focus on the T-cell response. Recent studies have shown that a broad repertoire of tumor-infiltrating HPV-specific T-cells are found in nearly all patients with HPV-positive tumors. A systemic response is found in only a proportion of these. Furthermore, the local response is more frequent in OPSCC patients than in cervical cancer patients and HPV-negative OPSCC patients. Despite this, tumor persistence may be facilitated by abnormalities in antigen processing, a skewed T-helper cell response, and an increased local prevalence of T-regulatory cells. Nonetheless, the immunologic profile of HPV-positive vs. HPV-negative HNSCC is associated with a significantly better outcome, and the HPV-specific immune response is suggested to play a role in the significantly better response to therapy of HPV-positive patients. Immunoprofiling may prove a valuable prognostic tool, and immunotherapy trials targeting HPV are underway, providing hope for decreasing treatment-related toxicity.

Baandrup, L., M. Blomberg, C. Dehlendorff, C. Sand, K. K. Andersen and S. K. Kjaer (2013). "Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program." Sex Transm Dis **40**(2): 130-135.

BACKGROUND: Approximately 90% of genital warts (GWs) are caused by human papillomavirus (HPV) types 6 and 11. Denmark has provided the quadrivalent HPV vaccine to all 12-year-old girls since 2009 and catch-up vaccination to girls up to 15 years since 2008, with up to 80% to 85% vaccine coverage. We determined the incidence of GWs in Denmark since 1996, focusing on the period after licensing of HPV vaccination (October 2006). METHODS: From the Danish National Patient Register, we identified all hospitalizations and outpatient consultations for GWs between January 1995 and July 2011. Poisson regression was used to estimate average annual percentage changes. RESULTS: The overall incidence of GWs in women increased significantly until 2007, followed by an average yearly decline of 3.1% (95%

confidence interval [CI], -5.5 to -0.7). In men, the incidence increased by 6.2% per year from 2004 (95% CI, 4.6-7.8). Stratifying on age, a significant decline was seen only for young women, particularly those aged 16 to 17 years, in whom GWs were virtually eliminated (average annual percentage change, -45.3%; 95% CI, -55.8 to -33.3). The incidences of genital Chlamydia, syphilis, and gonorrhea were stable or increased during the study period. CONCLUSIONS: The incidence of GWs decreased substantially among women with high HPV vaccine coverage, pointing to the effect of the national HPV vaccination program.

Baandrup, L., C. Munk, K. K. Andersen, J. Junge, T. Iftner and S. K. Kjaer (2012). "HPV16 is associated with younger age in women with cervical intraepithelial neoplasia grade 2 and 3." Gynecol Oncol **124**(2): 281-285.

OBJECTIVE: To evaluate if women with HPV16 positive CIN2 and CIN3 are diagnosed at a younger age. METHODS: We conducted a population-based cohort study including more than 40,000 women having a liquid based cervical cytology sample taken as part of routine screening. HPV analysis was performed using Hybrid Capture 2 and LiPAv2. The study population was linked to the Danish Pathology Data Bank to retrieve information on subsequent cervical histology. We included HR HPV positive CIN2/3 samples, comprising 173 CIN2 and 467 CIN3 lesions. Due to a high number of multiple concurrent HPV infections, the causative HPV type was assigned to a hierarchically group. RESULTS: In CIN3, the estimated proportion of lesions positive for HPV16 was 68.1% among women aged 20 years and decreased to 38.9% among women aged 50 years. A decrease in HPV16 positivity with increasing age was also observed in CIN2. In a multinomial logistic regression analysis, young age was strongly associated with HPV16 positivity in CIN3 lesions (OR=0.46 per 10 year increase in age, 95% CI: 0.32-0.65). The proportion of HPV16 and/or 18 positive lesions among women diagnosed with CIN2 and CIN3 below 30 years of age was 44% and 75%, respectively. CONCLUSIONS: HPV16 positivity was significantly associated with younger age at diagnosis of CIN3. In a population vaccinated against HPV16 and 18, we will experience a shift to older ages in cervical precancerous lesions. These findings may imply that cervical cancer screening programs could start at an older age in HPV vaccinated populations.

Baandrup, L., A. Varbo, C. Munk, C. Johansen, M. Frisch and S. K. Kjaer (2011). "In situ and invasive squamous cell carcinoma of the vulva in Denmark 1978-2007-a nationwide population-based study." Gynecol Oncol **122**(1): 45-49.

OBJECTIVE: To determine the incidence of vulvar carcinoma in situ (CIS) and cancer of squamous cell (SC) origin in Denmark in the period 1978-2007. METHODS: Using the nationwide Danish Cancer Registry, we identified 980 women diagnosed with vulvar CIS 1978-2003 (67.8% were SC) and 2455 women diagnosed with vulvar cancer 1978-2007 (76.0% were SC). Analysis was restricted to vulvar CIS and cancer of SC origin. We assessed age-specific incidence rates, age-standardized incidence rates, and distribution of stage at diagnosis. Poisson regression analysis was used to estimate the average annual percentage change. RESULTS: During the study period the age-standardized incidence rate of vulvar SC CIS increased by 1.97% per year (95% CI: 0.99% to 2.96%) with a tendency toward a steeper increase among women younger than 50 years. The age-standardized incidence rate of vulvar SC cancer showed a stable or slightly increasing pattern. However, among women below 60 years of age a significantly increasing trend was observed (1.60% per year; 95% CI: 0.50% to 2.71%). The distribution in the extent of vulvar SC cancer at diagnosis showed a tendency toward a higher proportion being diagnosed with localized disease in the more recent calendar years. CONCLUSIONS: The incidence rates of vulvar SC CIS and vulvar SC cancer among women below the age of 60 years have increased since 1978. Human papillomavirus (HPV) could explain the increase and thus, the recent introduction of HPV vaccination may in the future result in a notable reduction of vulvar malignancies.

Baldur-Felskov, B., C. Dehlendorff, J. Junge, C. Munk and S. K. Kjaer (2014). "Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program." Cancer Causes Control **25**(7): 915-922.

PURPOSE: Approximately 70% of cervical cancers and about 50% of high-grade cervical precursor lesions are caused by human papillomavirus (HPV) types 16 and 18. Denmark introduced the quadrivalent HPV vaccine into the vaccination program for 12-year-old girls in 2009 supplemented by a first catch-up program for 13-15-year-old girls in 2008, and a second program for women up to the age of 27 years in 2012; all with high vaccination coverage. The aim of this study was to evaluate the effectiveness of the vaccine by comparing the incidence trends of cervical lesions before and after its introduction. METHODS: Incident cases of cervical lesions were identified from the nationwide Pathology Data Bank. Age-specific incidence rates were estimated for six age groups, and Poisson regression was used to calculate estimated annual percentage change (EAPC). RESULTS: The incidence of atypia or worse (atypia+) and cervical intraepithelial neoplasia grade 2 or worse (CIN2+) increased in all age groups in 2000-2010. After introduction of the quadrivalent HPV vaccine into the vaccination program, the incidence of atypia+ decreased significantly in women younger than 18 years (EAPC -33.4%; 95% CI -49.6; -12.0) and in 18-20-year-old women (EAPC -12.6%; 95% CI -19.3; -5.3). The incidence of CIN2+ also decreased significantly in 18-20-year-old women (EAPC -14.8%; 95% CI -21.6; -7.5) in 2010-2013, but no significant decrease was seen in older age groups. CONCLUSION: The incidence of cervical lesions decreased significantly in age groups with high HPV vaccine coverage, indicating an early effect of HPV vaccination.

Baldur-Felskov, B., C. Dehlendorff, C. Munk and S. K. Kjaer (2014). "Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women." J Natl Cancer Inst **106**(3): djt460.

Baldur-Felskov, B., C. G. Hannibal, C. Munk and S. K. Kjaer (2012). "Increased incidence of penile cancer and high-grade penile intraepithelial neoplasia in Denmark 1978-2008: a nationwide population-based study." Cancer Causes Control **23**(2): 273-280.

OBJECTIVE: To assess the trends in incidence of penile cancer during 1978-2008 and high-grade penile intraepithelial neoplasia (PIN2/3) during 1998-2008 in Denmark. METHODS: Using two nationwide registries, we estimated age- and period-specific incidence rates. Log-linear Poisson regression analysis was used to estimate average annual percentage change (AAPC) and 95% confidence intervals (CI). RESULTS: We identified 1,488 men with penile cancer and 285 men with PIN2/3. The incidence of penile cancer increased from 1.0 to 1.3 per 100,000 men-years in 1978-1979 to 2006-2008; this represented an AAPC of 0.8% (95% CI: 0.17-1.37). Squamous cell carcinoma (SCC) was the most common histological type (91.7%). The median age at diagnosis was 67 years, and the age-specific incidence rate of penile SCC increased with increasing age. The incidence rate of PIN2/3 increased significantly (0.5 to 0.9 per 100,000 men-years) in 1998-1999 to 2006-2008, and this represented an AAPC of 7.1% (95% CI: 3.30-11.05). CONCLUSIONS: The incidence of penile cancer increased in 1978-2008 in Denmark, and the same applied to PIN2/3 in 1998-2008. A high prevalence of human papillomavirus (HPV) and a low circumcision rate in Denmark may partly explain our results.

Baldur-Felskov, B., C. Munk, T. S. Nielsen, C. Dehlendorff, B. Kirschner, J. Junge and S. K. Kjaer (2015). "Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012." Cancer Causes Control **26**(8): 1105-1116.

PURPOSE: The incidence of cervical cancer, including squamous cell carcinoma (SCC), has been decreasing in several developed countries since the onset of organized screening programs; in some countries, however, the incidence of adenocarcinoma has increased among young women. We investigated the Danish incidence trends during 1997-2011 when cervical screening coverage was high.

Incidences of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) were also assessed, with the latest part of the study period coinciding with introduction of free-of-charge human papillomavirus (HPV) vaccination. METHODS: Using nationwide registries, we estimated age-specific and age-standardized incidence rates and estimated annual percentage change (EAPC). RESULTS: The incidence of SCC decreased significantly, especially in women aged >/=45 years [EAPC: -3.1 % (95 % CI -4.3 to -2.5)], whereas the incidence of adenocarcinoma increased significantly, from 2.4 to 3.1/100,000 primarily due to increases in women aged </=44 years [EAPC: 4.3 % (95 % CI 1.8-6.7)]. The incidences of CIN3 and AIS increased significantly from 94.7 to 156.5/100,000 and 3.3 to 11.3/100,000, respectively, but, importantly, they decreased significantly during 2009-2012 in women aged </=20 years. CONCLUSIONS: The Danish screening program has successfully reduced the incidence of cervical cancer, especially of SCC in older women; however, the program has not significantly reduced the incidence in young women or the incidence of adenocarcinoma, which is increasing. Decreases in the incidences of CIN3 and AIS in age groups with high HPV vaccine coverage may herald a future decrease in cervical cancer incidence in young Danish women.

Blomberg, M., C. Dehlendorff, C. Munk and S. K. Kjaer (2013). " Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated girls in Denmark." Clin Infect Dis **57**(7): 929-934.

BACKGROUND: A reduction in the incidence of genital warts (GWs) is one of the first markers of the effectiveness of vaccination against human papillomavirus (HPV) at the population level. The aim of this cohort study was to use individual information on HPV vaccination status to assess the effect on risk of GWs. METHODS: Population-based registries were used to identify all girls in the birth cohorts 1989-1999 in Denmark, and information about HPV vaccination was obtained for the period 2006-2012. The cohort was linked to incident cases of GWs, and vaccinated and unvaccinated girls were compared using Cox proportional hazards models. RESULTS: A total of 248 403 girls were vaccinated. The relative risk of GWs among girls who had received at least 1 dose of vaccine compared with unvaccinated girls was 0.12, 0.22, 0.25, and 0.62 for those born in 1995-1996, 1993-1994, 1991-1992, and 1989-1990, respectively (P for trend < .0001). No GWs occurred among vaccinated girls in the youngest birth cohort (1997-1999). CONCLUSIONS: The strong, highly significant reduction in the occurrence of GWs among vaccinated girls indicates an early and marked population effect of the national HPV vaccination program and may forecast a similar effect on cervical precancerous lesions.

Blomberg, M., C. Dehlendorff, C. Sand and S. K. Kjaer (2015). "Dose-Related Differences in Effectiveness of Human Papillomavirus Vaccination Against Genital Warts: A Nationwide Study of 550,000 Young Girls." Clin Infect Dis **61**(5): 676-682.

BACKGROUND: Reducing the number of doses in the human papillomavirus (HPV) vaccination regimen from 3 to 2 could increase coverage rates. In this cohort study, we assessed the risk of genital warts (GWs) according to timing and number of doses of quadrivalent HPV vaccine. METHODS: From population-based registries, we identified all girls in Denmark born during 1985-1999, for whom information on HPV vaccinations was retrieved. The cohort was followed for GW occurrence during 2006-2012. Incidence rate ratios (IRRs) were calculated by Poisson regression to determine differences in GW rates by number of vaccine doses. RESULTS: Of the 550,690 girls in the cohort, 361 734 had been vaccinated. Of these, 25.9% had been vaccinated twice and 58.8% 3 times. The risk of GWs decreased significantly with each additional dose of vaccine. For girls who received 2 doses, extension of the interval between doses reduced the incidence of GWs. In comparison with a 2-month interval, the incidence of GWs was reduced by 45% (95% confidence interval [CI], 20%-62%), 55% (95% CI, 35%-69%), and 63% (95% CI, 44%-75%), with an interval of 4, 5, and 6 months, respectively. The IRR of 2 vs 3 doses was close to 1, with an interval of about 6 months between the first 2 doses. CONCLUSIONS: With the original vaccine

schedule, completion of 3 doses seems to be required to obtain full protection against GWs. A 2-dose regimen may be as effective if the dosing interval is extended to around 6 months, although the long-term effectiveness of this regimen is unknown.

Blomberg, M., S. Friis, C. Munk, A. Bautz and S. K. Kjaer (2012). "Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts." J Infect Dis **205**(10): 1544-1553.

BACKGROUND: We conducted a large national cohort study to examine the risk of cancer among men and women with genital warts (GW). METHODS: By use of the Danish National Patient Register, we identified 16,155 men and 32,933 women who received a diagnosis of GW during 1978-2008. Standardized incidence ratios (SIRs) were computed as estimates of the relative risk of specific cancers or sites. RESULTS: A diagnosis of GW was strongly related to anal (SIR for men, 21.5; SIR for women, 7.8), vulvar (SIR, 14.8), vaginal (SIR, 5.9), cervical (SIR, 1.5), penile (SIR, 8.2), and head and neck cancer (SIR, 2.8), including subsites of head and neck cancer with confirmed HPV association (SIR for men, 3.5; SIR for women, 4.8). The risks remained elevated for >10 years following GW diagnosis. In addition, we found moderately increased SIR estimates for nonmelanoma skin cancer, smoking-related cancers, and Hodgkin and non-Hodgkin lymphoma. CONCLUSIONS: Individuals with GW have a long-term increased risk of anogenital cancers and head and neck cancers. The elevated risks of nonmelanoma skin cancers might indicate an association with HPV, while excess risks of other cancers could point to differences in other risk factors between individuals with GW and the general population.

Blomberg, M., A. Nielsen, C. Munk and S. K. Kjaer (2011). "Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites." Int J Cancer **129**(3): 733-741.

The aim of our study was to assess the overall trends in the incidence of head-and-neck cancer (HNC) among Danish men and women in 1978-2007, to describe the distribution and incidences of HNCs at different anatomical sites, and to determine whether the incidence of human papillomavirus (HPV)-associated cancers is increasing. Data were extracted from the nationwide Cancer Registry database. To assess the possible impact of HPV infection, the sites of squamous cell carcinomas were categorized as HPV-associated, potentially HPV-associated or HPV-unrelated. In total, 26,474 incident cases were identified and the overall incidence increased throughout the period. Significantly increasing incidence rates were notably seen for tumors in the oral cavity (2.2% per year), tonsils (4.8% per year), oropharynx (3.5% per year) and hypopharynx (4.4% per year). A significantly decreasing incidence of lip cancer was observed among men (-5.0% per year). Cancers at HPV-associated sites (n = 3650) showed strongly increasing incidence rates, primarily in individuals < 60 years. In contrast, HNCs at sites not related to HPV infection showed a significant decrease (in men) or virtually no change in incidence (in women). Our results suggest a marked impact of HPV infection on the epidemiology of HNCs in Denmark. HPV16 is the type most often found in HNCs; thus, the recent introduction of vaccination against HPV may in the future prevent HPV-associated cancers of the head and neck.

Bonde, J., M. Rebolj, D. M. Ejegod, S. Preisler, E. Lynge and C. Rygaard (2014). "HPV prevalence and genotype distribution in a population-based split-sample study of well-screened women using CLART HPV2 human papillomavirus genotype microarray system." BMC Infect Dis **14**: 413.

BACKGROUND: Human papillomavirus (HPV) genotyping assays are becoming increasingly attractive for use in mass screening, as they offer a possibility to integrate HPV screening with HPV vaccine monitoring, thereby generating a synergy between the two main modes of cervical cancer prevention. The Genomica CLART HPV2 assay is a semi-automated PCR-based microarray assay detecting 35 high-risk and low-risk HPV genotypes. However, few reports have described this assay in cervical screening. An aim of the present study, Horizon, was to assess the prevalence of high-risk HPV infections in Copenhagen, Denmark, an area with a high background risk of cervical cancer where women aged 23-65 years are

targeted for organized screening. METHODS: Material from 5,068 SurePath samples of women participating in routine screening and clinical follow-up of cervical abnormalities was tested using liquid based cytology, CLART HPV2 and Hybrid Capture 2 (HC2). RESULTS: At least one of the 35 defined genotypes was detected by CLART in 1,896 (37%) samples. The most frequent high-risk genotypes were HPV 16 (7%), HPV 52 (5%), and HPV 31 (4%). The most frequent low-risk genotypes were HPV 53 (5%), HPV 61 (4%), and HPV 66 (3%). Among 4,793 women targeted by the screening program (23-65 years), 1,166 (24%) tested positive for one or more of the 13 high-risk genotypes. This proportion decreased from 40% at age 23-29 years to 10% at age 60-65 years. On HC2, 1,035 (20%) samples were positive for any high-risk and thus CLART showed a higher analytical sensitivity for 13 high-risk HPV genotypes than HC2, and this was found in all age-groups and in women normal cytology. CONCLUSIONS: CLART performed well with a positive reproducibility for high-risk genotypes of 86%, and a negative reproducibility of 97%. This report furthermore updates the genotype distribution in Denmark prior to the inclusion of the HPV-vaccinated cohorts into the screening program, and as such represents a valuable baseline for future vaccine impact assessment.

Brogaard, K. A., C. Munk, T. Iftner, K. Frederiksen and S. K. Kjaer (2014). " Detection of oncogenic genital human papillomavirus (HPV) among HPV negative older and younger women after 7 years of follow-up." J Med Virol **86**(6): 975-982.

The knowledge on risk factors of being human papillomavirus (HPV)-positive among older women is sparse. The aim was to determine the frequency of oncogenic HPV appearance after 7 years among initially HPV-negative women and to examine potential risk factors that influence the occurrence of HPV in older women using multiple logistic regression. For comparison, a younger cohort of women examined under identical study settings was included. This prospective cohort study comprised 1,577 older women (age 40-50 at enrolment) and 2,920 women aged 22-32. Participants were interviewed and underwent a gynecological examination at two time points (7 years apart). Cervical samples were tested for HPV using Hybrid Capture 2 (HC2) and only women who tested HC2-negative at baseline were included. The HPV prevalence among older and younger women was 6.4% and 10.7%, respectively, and there was no "second peak" observed among older women. Recent sexual partners were a strong determinant of HPV appearance irrespective of age. Lifetime number of sexual partners was a significant risk factor for HPV appearance among older women, even after adjustment for recent sexual behavior. In addition, menopause was associated with a non-significantly increased risk of HPV appearance at follow-up. In conclusion, appearance of HPV in previously HPV-negative older women may be due to both recent sexual behavior and previous exposure that is, reactivation of a latent HPV infection.

Dreyer, L., M. Faurschou, M. Mogensen and S. Jacobsen (2011). "High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort." Arthritis Rheum **63**(10): 3032-3037.

OBJECTIVE: Patients with systemic lupus erythematosus (SLE) seem to experience an increased prevalence of oncogenic virus infections. The aim of the present study was to investigate whether SLE patients have an increased risk of virus-associated malignancies, defined as malignancies potentially caused by virus infection. METHODS: A hospital-based cohort of 576 SLE patients was linked to the Danish Cancer Registry. The cohort was followed up for malignancies from the date of SLE diagnosis, and standardized incidence ratios (SIRs) were calculated for various forms of cancer. RESULTS: The median duration of followup was 13.2 years. Compared to the general population, the patients experienced an increased overall risk of cancer (SIR 1.6 [95% confidence interval (95% CI)] 1.2-2.0). We observed an increased risk of virus-associated cancers combined (SIR 2.9 [95% CI 2.0-4.1]). Among human papillomavirus (HPV)-associated malignant and premalignant conditions, high risk was found for anal cancer (SIR 26.9 [95% CI 8.7-83.4]), vaginal/vulvar cancer (SIR 9.1 [95% CI 2.3-36.5]), epithelial

dysplasia/carcinoma in situ of the uterine cervix (SIR 1.8 [95% CI 1.2-2.7]), and nonmelanoma skin cancer (SIR 2.0 [95% CI 1.2-3.6]). Increased SIRs were also found for other potentially virus-induced cancer types (liver cancer SIR 9.9 [95% CI 2.5-39.8], bladder cancer SIR 3.6 [95% CI 1.4-9.7], and non-Hodgkin's lymphoma SIR 5.0 [95% CI 1.9-13.3]). CONCLUSION: The patients in this SLE cohort experienced an increased risk of HPV-associated tumors and other potentially virus-induced cancers during long-term followup. Our findings call for clinical alertness to oncogenic virus infections in SLE patients.

Dugue, P. A., E. Lynge and M. Rebolj (2014). "Mortality of non-participants in cervical screening: Register-based cohort study." Int J Cancer **134**(11): 2674-2682.

The selective uptake of screening by healthy participants and its impact on the evaluation of screening effectiveness in non-randomized studies have been discussed, but hardly studied. We quantified excess mortality among cervical screening non-participants compared to participants. Based on Danish healthcare registers, we determined women's participation in cervical screening in 1990-1993 (one screening round) and 1990-1997 (two screening rounds). Women were followed until end of 2010. We computed hazard ratios (HR) comparing non-participants' and participants' risk of death, and analyzed the impact of age, calendar period of screening evaluation, screening intensity, length of follow-up and cause of death. After one screening round, the 17-year HR of death in non-participants was 1.61 (95% CI: 1.59-1.63), with an increasing trend over calendar time. After two rounds, regular non-participants had a HR of 2.09 (95% CI: 2.05-2.14) compared to regular participants. The HR for human papillomavirus (HPV)-related cancers other than cervical cancer was 3.80 (95% CI: 2.67-5.41). Younger women, whose coverage rates were higher, had higher all-cause mortality HRs. Women screened more frequently than recommended had the same mortality as those screened as recommended. Acute illness did not seem to be a major reason for non-participation, as the excess risk of death was not higher in the first years following screening evaluation. Non-participants in cervical screening had substantially higher all-cause mortality than participants, and a particularly increased risk of HPV-related causes of death. These results indicate that improper control for the selective uptake of cervical screening may result in overestimating its effectiveness.

Forslund, O., H. Johansson, K. G. Madsen and K. Kofoed (2013). "The nasal mucosa contains a large spectrum of human papillomavirus types from the Betapapillomavirus and Gammapapillomavirus genera." J Infect Dis **208**(8): 1335-1341.

BACKGROUND: Human papillomavirus (HPV) types from the Betapapillomavirus and Gammapapillomavirus genera are common at cutaneous sites. The aim of this study was to analyze the prevalence of these HPV types in oral and nasal samples. METHODS: Nasal samples and oral samples were obtained from 312 volunteer Danish healthcare staff (240 women and 72 men), among whom the mean age was 42 years. A total of 311 oral samples and 304 nasal samples were eligible for HPV DNA analysis. HPV types were detected by use of polymerase chain reactions with modified general primers (MGP) and Forslund-Antonsson primers (FAP) and identified by Luminex (for types detected by MGP PCR) or direct sequencing or cloning before sequencing (for types detected by FAP PCR). RESULTS: HPV DNA was detected in 6% of the oral samples and 50% of the nasal samples. Seventy-five diverse HPV types or putative HPV types were identified. HPV types within the Alphapapillomavirus, Betapapillomavirus, and Gammapapillomavirus genera were detected in 3%, 31%, and 23% of the nasal samples, respectively. A putative subtype of HPV76, originally isolated from a feline oral squamous cell carcinoma, was detected in 7 nasal samples. CONCLUSION: A large spectrum of HPV types from Betapapillomavirus and Gammapapillomavirus have tropism for the nasal mucosa. The implication of the relatively high prevalence of these viruses in the nasal mucosa is unknown.

Garnaes, E., K. Kiss, L. Andersen, M. H. Therkildsen, M. B. Franzmann, B. Filtenborg-Barnkob, E. Hoegdall, L. Krenk, M. Josiassen, C. B. Lajer, L. Specht, K. Frederiksen, L. Friis-Hansen, F. C. Nielsen, S. K. Kjaer, B. Norrild and C. von Buchwald (2015). "A high and increasing HPV prevalence in tonsillar cancers in Eastern Denmark, 2000-2010: the largest registry-based study to date." Int J Cancer **136**(9): 2196-2203.

The aim was to explore whether the incidence of tonsillar squamous cell carcinomas (TSCCs) increased in Eastern Denmark, 2000-2010, and whether human papillomavirus (HPV) could explain the increase, and to assess the association of HPV prevalence with gender, age, and origin (i.e., the certainty of tonsillar tumor origin). We applied HPV DNA PCR and p16 immunohistochemistry to all TSCCs registered in the Danish Head and Neck Cancer Group (DAHANCA) and in the Danish Pathology Data Bank (n = 632). Pathologists reviewed and subdivided the tumors into two groups: specified and nonspecified TSCCs. Approximately 10% of HPV-positive tumors was genotyped by amplicon next-generation sequencing. The overall crude incidence of TSCCs increased significantly (2.7% per year) and was explained by an increasing incidence of HPV-positive TSCCs (4.9% per year). The overall HPV prevalence was 58%, with HPV16 being the predominant HPV type. In multivariate analysis, the HPV prevalence was associated with age (<55 vs. >60 years) (OR, 1.72; 95% CI 1.13-2.63) and origin (nonspecified vs. specified TSCCs) (OR, 0.15; 95% CI 0.11-0.22). The association of HPV prevalence with origin increased over time in specified TSCCs (OR per year, 1.10; 95% CI 1.01-1.19), whereas no change over time was observed among nonspecified TSCCs (OR per year, 0.99; 95% CI 0.90-1.08). In conclusion, the observed increase in the number of HPV-positive TSCCs can explain the increasing number of TSCCs in Eastern Denmark, 2000-2010. HPV prevalence was associated with younger age (<55 years) and a high certainty of tonsillar tumor origin.

Garnaes, E., K. Kiss, L. Andersen, M. H. Therkildsen, M. B. Franzmann, B. Filtenborg-Barnkob, E. Hoegdall, C. B. Lajer, E. Andersen, L. Specht, L. Joenson, K. Frederiksen, L. Friis-Hansen, F. C. Nielsen, S. K. Kjaer, B. Norrild and C. von Buchwald (2015). "Increasing incidence of base of tongue cancers from 2000 to 2010 due to HPV: the largest demographic study of 210 Danish patients." Br J Cancer **113**(1): 131-134.

BACKGROUND: We assessed the development in the number of new base of tongue squamous-cell carcinoma (BSCC) cases per year in eastern Denmark from 2000 to 2010 and whether HPV may explain any observable increased incidence. METHODS: We performed HPV DNA PCR and p16 immunohistochemistry analysis for all (n=210) BSCCs registered in the Danish Head and Neck Cancer Group (DAHANCA) and the Danish Pathology Data Bank, and genotyped all HPV-positive specimens with amplicon-based next-generation sequencing. RESULTS: The overall crude incidence of BSCCs increased significantly (5.4% per year) during the study period. This was explained by a significant increase in the number of HPV-positive BSCCs (8.1% per year), whereas the number of HPV-negative BSCCs did not increase significantly. The overall HPV prevalence was 51%, with HPV16 as the predominant HPV type. CONCLUSIONS: The increased number of HPV-positive BSCCs may explain the increasing incidence of BSCCs in eastern Denmark, 2000-2010.

Goldman, B., M. Rebolj, C. Rygaard, S. Preisler, D. M. Ejegod, E. Lynge and J. Bonde (2013). "Patterns of cervical coinfection with multiple human papilloma virus types in a screening population in Denmark." Vaccine **31**(12): 1604-1609.

Patterns of cervical human papillomavirus (HPV) infection suggest that HPV genotypes are not independent of each other. This may be explained by risk factors common to all HPV infections, but type-specific biological factors may also play a role. This raises the question of whether widespread use of the quadrivalent vaccine (covering HPV6, 11, 16, 18) may indirectly affect the prevalence of any non-vaccine types. Routine screening samples from 5014 Danish women were tested for 35 HPV genotypes (including 13 high-risk) using the Genomica CLART((R)) HPV2 kit, which is a low-density microarray based on PCR amplification. Simulation studies were performed both under independence between genotypes and under a common dependence structure as would arise from common risk factors, and simulation results

were compared to observed coinfection patterns. Overall HPV prevalence was 37.4%, with multiple infections in 17.9%. For 15 HPV types of primary interest (13 high-risk plus HPV6, 11), almost all pairs occurred more often than expected under independence; 33/105 (31.4%) were statistically significant ($p<0.05$ after adjustment for multiple comparisons). The pairwise odds ratios showed significant heterogeneity (Woolf's test $p<0.0001$). For simulations based on common dependence, three pairs had observed to expected (O/E) ratios significantly different than 1 (31/68, O/E=4.20; 51/68, O/E=2.52; 33/58, O/E=3.27; all $p<0.05$ after adjustment for multiple comparisons). HPV68 occurred in multiple infections nearly four times as often as expected under common dependence ($p<0.005$ after adjustment for multiple comparisons). These results indicate some interaction between HPV types, and suggest that common risk factors do not entirely explain the observed HPV coinfection pattern, although no evidence is found that the prevalence of any types not targeted by the quadrivalent vaccine may be indirectly increased or decreased after widespread use of the vaccine.

Hammer, A., E. Mejlgaard, P. Gravitt, E. Hogdall, P. Christiansen, T. Steiniche and J. Blaakaer (2015). "HPV genotype distribution in older Danish women undergoing surgery due to cervical cancer." Acta Obstet Gynecol Scand **94**(11): 1262-1268.

INTRODUCTION: The prevalence of human papillomavirus (HPV)16/18 in cervical cancer may decrease with age. This study aimed to describe the HPV genotype distribution in Danish women aged 55 years or older with cervical cancer. MATERIAL AND METHODS: In this cross-sectional study we identified 153 cases of cervical cancer diagnosed at Aarhus University Hospital, Denmark (1990-2012) and Copenhagen University Hospital Herlev, Denmark (2007-2012). All women had surgery to treat the disease. HPV genotyping was performed on cervical cancer tissue using the INNO LiPA HPV genotyping extra (Fujirebio, Belgium) at the Department of Pathology, Aarhus University Hospital, Denmark. The main outcome was to estimate the age-specific prevalence of high-risk HPV genotypes included in the bivalent, the quadrivalent, and the nonavalent vaccine. RESULTS: Of 121 cases of cervical cancer included in this study, 113 were HPV-positive (93.4%). Although HPV16 and 18 were the most common genotypes overall, the prevalence of HPV16/18 decreased significantly from 78.1% in women aged 55-59 years to 45.5% in women aged 75 or older ($p < 0.001$), whereas the prevalence of other HPV types and HPV-negative cases tended to increase with age ($p = 0.1$). The prevalence of HPV types included in the nonavalent vaccine was stable around 90% until the age of 75 years and then dropped to 63%. CONCLUSION: In the absence of waning immunity, the nonavalent HPV vaccine would be predicted to reduce cervical cancer burden in Denmark across a broader age-range compared with the reduced type-spectrum vaccines.

Hebnes, J. B., C. Munk, B. Nohr, A. Nielsen, H. O. Jorgensen, T. Iftner and S. K. Kjaer (2015). "Human Papillomavirus Infection Among 2460 Men in Denmark: Prevalence in Relation to Age Using 2 Human Papillomavirus DNA Testing Methods." Sex Transm Dis **42**(8): 463-467.

BACKGROUND: It is crucial to understand the epidemiology and natural history of human papillomavirus (HPV) infection in both men and women, to prevent the increasing HPV-related disease burden in men. Data on HPV prevalence among men in the general population are limited. In this cross-sectional population-based study, we aimed to estimate genital HPV infection prevalence in Danish men using 2 different test methods. METHODS: Penile swab samples from 2460 male employees and conscripts at military barracks in Denmark were tested for HPV DNA with the hybrid capture 2 (HC2) method, and a polymerase chain reaction (PCR) assay, Inno-LiPA. The overall and age- and type-specific prevalence of HPV infection with 95% confidence intervals (CIs) were estimated, and the correlation between the 2 assays was assessed. RESULTS: The overall HPV prevalence was 22.2% (95% CI, 20.6-23.9) in the HC2 test and 41.8% (95% CI, 39.9-43.8) with PCR. Of the PCR-positive samples, 50.9% were negative in the HC2 test. Of 183 PCR-positive samples that could not be genotyped (HPVX), 88.0% (95% CI, 83.2-92.7) were HC2 negative. The most prevalent types were HPV-51, HPV-16, HPV-66, HPV-53, and HPV-6. The

prevalence of high-risk and low-risk HPV peaked among men aged 20 to 29 years, whereas the HPVX prevalence increased with age. CONCLUSIONS: Human papillomavirus is highly prevalent in the general male population of Denmark, with HPV-16 and HPV-51 being the most prevalent. Polymerase chain reaction detects twice as many positive samples as HC2 but includes HPVX, possibly representing cutaneous HPV types found on normal genital skin.

Jensen, D. H., N. Hedback, L. Specht, E. Hogdall, E. Andersen, M. H. Therkildsen, L. Friis-Hansen, B. Norrild and C. von Buchwald (2014). "Human papillomavirus in head and neck squamous cell carcinoma of unknown primary is a common event and a strong predictor of survival." PLoS One **9**(11): e110456.

BACKGROUND: The purpose of this study was to examine the prevalence of human papillomavirus (HPV) in patients with head and neck squamous cell carcinoma of unknown primary (CUP). METHODS: All patients diagnosed with and treated for CUP between January 1, 2000, and June 1, 2011, at two Danish medical centers were included. All patients received a thorough diagnostic work-up, including FDG-PET, before being diagnosed as CUP. We determined the HPV status in all patients using a combination of HPV DNA PCR and p16 stain. In addition, clinical information on the study patients was retrieved from clinical records. RESULTS: Of the identified 60 patients with CUP, 13 were shown to be positive for HPV DNA, amounting to 22% of the study population. In addition, we were able to show a clear disease-free and overall-survival benefit in the HPV-positive group, with a hazard ratio of 0.16 (95% CI: 0.038-0.67) for overall survival. This survival benefit was also apparent when adjusted for advanced age in a multivariate Cox regression analysis. CONCLUSION: A fairly large percentage of CUP cases are HPV-related, and because this is related to both the location and prognosis, we recommend HPV testing as part of the diagnostic work-up.

Jensen, K. E., S. Schmiedel, K. Frederiksen, B. Norrild, T. Iftner and S. K. Kjaer (2012). "Risk for cervical intraepithelial neoplasia grade 3 or worse in relation to smoking among women with persistent human papillomavirus infection." Cancer Epidemiol Biomarkers Prev **21**(11): 1949-1955.

BACKGROUND: Smoking has been associated with cervical cancer. We examined whether smoking increases the risk for high-grade cervical lesions in women with high-risk human papillomavirus (HPV) infection. METHODS: In a population-based cohort study, 8,656 women underwent a structured interview, and subsequently cervical cells were obtained for HPV DNA testing. Women with high-risk HPV infection and no prevalent cervical disease at baseline (n = 1,353) were followed through the Pathology Data Bank for cervical lesions for up to 13 years. Separate analyses of women with persistent high-risk HPV infection (n = 312) were also conducted. HRs for a diagnosis of cervical intraepithelial neoplasia grade 3 or worse/high-grade squamous intraepithelial lesions or worse (CIN3+) and the corresponding 95% confidence intervals (CI) were calculated in the two groups. RESULTS: Among high-risk HPV-positive women, an increased risk for CIN3+ was associated with long-term smoking (>/=10 years) and heavy smoking (>/=20 cigarettes/d). In the subgroup of women with persistent HPV infection, heavy smoking was also associated with a statistically significantly higher risk for CIN3+ than never smoking (HR, 1.85; 95% CI, 1.05-3.22, adjusted for length of schooling, parity, and HPV type at baseline). The average number of cervical cytology screening tests per year during follow-up did not explain the differences in risk in relation to smoking (P = 0.4). CONCLUSIONS: Smoking is associated with an increased risk for subsequent high-grade cervical lesions in women with persistent high-risk HPV infection. IMPACT: Our study adds to the understanding of the role of smoking in the natural history of HPV and cervical carcinogenesis.

Jensen, K. E., L. T. Thomsen, S. Schmiedel, K. Frederiksen, B. Norrild, A. van den Brule, T. Iftner and S. K. Kjaer (2014). "Chlamydia trachomatis and risk of cervical intraepithelial neoplasia grade 3 or worse in women with persistent human papillomavirus infection: a cohort study." Sex Transm Infect **90**(7): 550-555.

OBJECTIVES: Some studies suggest that Chlamydia trachomatis (CT) enhances cervical carcinogenesis; however, a possible confounding effect of persistent human papillomavirus (HPV) infection was not addressed. We examined the potential role of CT infection in the development of subsequent cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in women with prevalent HPV infection and in a subgroup of women with persistent HPV infection. METHODS: Participants in this population-based cohort study underwent a structured interview, including history of CT infection, and subsequently cervical exfoliated cells were obtained for HPV DNA and CT DNA testing. Women with high-risk HPV DNA infection and no prevalent cervical disease constituted the overall study population (n=1390). A subgroup of women with persistent HPV infection (n=320) was also identified. All women were passively followed for development of cervical lesions in the national Pathology Data Bank. HRs and 95% CIs for CIN3+ during follow-up (up to 19 years) were estimated in an accelerated failure time model. RESULTS: Women who reported more than one CT infection had a statistically significantly increased risk of CIN3+ (high-risk HPV-positive, HR=2.51, 95% CI 1.44 to 4.37) (persistent HPV infection, HR=3.65, 95% CI 1.53 to 8.70). We found no association between CT DNA and subsequent risk of CIN3+ among women who were HPV-positive or had a persistent HPV infection at baseline. CONCLUSIONS: Repeated CT infections increased the risk of CIN3+ among women with prevalent as well as persistent high-risk HPV infection.

Kiellberg Larsen, H., K. Kofoed and C. Sand (2013). "[The disease burden of human papillomavirus in men is substantial and can potentially be prevented]." Ugeskr Laeger **175**(6): 349-353.

Human papillomavirus (HPV) is a highly prevalent sexually transmitted infection. High-risk HPV causes penile cancer and a substantial proportion of oropharyngeal and anal malignancy in men. Low-risk types of HPV cause anogenital warts. The incidence of oropharyngeal and anal cancers is increasing in Denmark. Prevention of penile, anal and oropharyngeal cancers and anogenital warts represents potential benefits of the HPV vaccine; and vaccination of men is now recommended by the Australian and the North American health authorities. Thus, we recommend that the Danish HPV vaccination program should include men.

Kirkegard, J., D. K. Farkas, M. Sogaard, S. A. Schmidt, E. B. Ostenfeld and D. Cronin-Fenton (2014). "Conization as a marker of persistent cervical human papillomavirus (HPV) infection and risk of gastrointestinal cancer: a Danish 34-year nationwide cohort study." Cancer Causes Control **25**(12): 1677-1682.

PURPOSE: Persistent cervical infection with human papillomavirus (HPV) may be a marker of poor immune function and thus associated with an increased cancer risk. HPV infection is implicated in all cases of cervical cancer, but except for anal and esophageal cancers, the association between persistent HPV infection and gastrointestinal cancer has not been investigated. METHODS: We performed a nationwide population-based cohort study of 83,008 women undergoing cervical conization between 1978 and 2011, using cervical conization as a marker of chronic HPV infection. We computed standardized incidence ratios (SIRs) as a measure of the relative risk of each cancer comparing women undergoing conization with that expected in the general population. We also calculated absolute risks. RESULTS: During follow-up, 988 GI cancers occurred versus 880 expected among 83,008 women followed for a median of 14.9 years, corresponding to a SIR of 1.1 (95 % CI 1.1-1.2). Risks were increased for anal (SIR 2.9; 95 % CI 2.3-3.5) and esophageal (SIR 1.5; 95 % CI 1.1-2.0) cancers, with suggested increased risks of cancers of the gallbladder and biliary tract (SIR 1.3; 95 % CI 0.90-1.8), pancreas (SIR 1.2; 95 % CI 0.97-1.4), and liver (SIR 1.1; 95 % CI 0.79-1.6). The SIRs decreased with increasing follow-up time. The risks of gastric, small intestinal, colon, or rectal cancers were not elevated. Overall, the absolute cancer risk was 0.18 % (95 % CI 0.15-0.21) after 5 years. CONCLUSIONS: The relative risks of several gastrointestinal cancers were raised among women who underwent cervical conization for persistent HPV infection, but the absolute risks were low.

Kjaer, S. K., G. Breugelmans, C. Munk, J. Junge, M. Watson and T. Iftner (2008). "Population-based prevalence, type- and age-specific distribution of HPV in women before introduction of an HPV-vaccination program in Denmark." Int J Cancer **123**(8): 1864-1870.

Knowledge about the prevalence of human papillomavirus (HPV) on a population level is important. We conducted a large population-based study in Denmark to determine the overall and age-specific HPV prevalence, and HPV type distribution in women. Liquid-based cytology samples (SurePath) were collected consecutively. HPV testing was performed with Hybrid Capture 2 (HC2; Digene) (high-risk and low-risk probes), and LiPA (Innogenetics) was used for genotyping. We analyzed samples from 11,617 women; 94.0% had normal cytology, 4.3% atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion and 1.6% had high-grade squamous intraepithelial lesion (HSIL). The HPV prevalence was 26.4% with a peak in women 20-24 years (50.2%) and then decreased without a second peak in older women. Among the youngest women (15-19 years), 14% had HPV 16/18 and 16% had HPV 6/11. Prevalence of high-risk HPV types increased from 19.2% in women with normal cytology to 100% in women with cervical intraepithelial neoplasia grade 3 (CIN3)/cervical cancer. HPV 16 was the most prevalent type (6.0% of all women), and was also the most prevalent in women with HSIL (35.1%) and CIN3 (53.2%). Other common HPV types in women with CIN3 included HPV 52, 51, 31, 33 and 18. HPV 16/18 alone was present in 23% of CIN3 lesions and 67% of cervical cancers, and HPV 16/18 together with other high-risk HPV types was present in 41% of CIN3 lesions. This suggests that an efficacious HPV 16/18 vaccine will have a substantial preventive potential in the general female population.

Kjaer, S. K., C. Munk, J. Junge and T. Iftner (2014). "Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention?" Cancer Causes Control **25**(2): 179-189.

Kjaer, S. K., T. N. Tran, P. Sparen, L. Tryggvadottir, C. Munk, E. Dasbach, K. L. Liaw, J. Nygard and M. Nygard (2007). "The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries." J Infect Dis **196**(10): 1447-1454.

OBJECTIVE: To assess the burden and correlates of genital warts in women. METHODS: We conducted a population-based cross-sectional study in 69,147 women (18-45 years of age) randomly chosen from the general population in Denmark, Iceland, Norway, and Sweden. Information on clinically diagnosed genital warts and lifestyle habits was collected using a questionnaire. RESULTS: Overall, 10.6% reported ever having had clinically diagnosed genital warts. In addition, 1.3% reported having experienced genital warts within the past 12 months. The cumulative incidence for different birth cohorts, estimated on the basis of age at first diagnosis of genital warts, increased with each subsequent younger birth cohort (P<.01). The lifetime number of sex partners was strongly correlated with a history of genital warts (odds ratio for > or =15 partners vs. 1 partner, 9.45 [95% confidence interval, 7.89-11.30]). The likelihood of reporting genital warts also increased with a history of sexually transmitted disease, use of hormonal contraceptives, use of condoms, smoking, and higher education. CONCLUSIONS: The data suggest that 1 in 10 women in the Nordic countries experience genital warts before the age of 45 years, with an increasing occurrence in younger birth cohorts. These data are important for developing and evaluating strategies (e.g., human papillomavirus [HPV] vaccination) to control and prevent HPV infection and disease in the population.

Kofoed, K., C. Sand, O. Forslund and K. Madsen (2014). "Prevalence of human papillomavirus in anal and oral sites among patients with genital warts." Acta Derm Venereol **94**(2): 207-211.

Genital warts are caused by human papillomavirus (HPV). HPV is a leading cause of anogenital malignancies and a role of HPV in the aetiology of oro-pharyngeal cancers has been demonstrated. The

frequency of oral HPV infection in patients with genital warts and the association between concomitant genital, anal and oral infection is unclear. A total of 201 men and women with genital wart-like lesions were recruited. Swab samples were obtained from the genital warts and the anal canal and an oral rinse was collected. Anal HPV was found in 46.2% and oral HPV in 10.4% of the participants. Concordance between anal and genital wart HPV types was 78.1%, while concordance between oral and genital wart types was 60.9%. A lower concordance of 21.7% was observed between anal and oral HPV types. Significantly more women than men had multiple HPV types and anal HPV. In conclusion, extra genital HPV is common in patients with genital warts. A gender inequality seems to exist.

Madsen, B. S., H. L. Jensen, A. J. van den Brule, J. Wohlfahrt and M. Frisch (2008). "Risk factors for invasive squamous cell carcinoma of the vulva and vagina--population-based case-control study in Denmark." Int J Cancer **122**(12): 2827-2834.

The etiology of vulvar and vaginal squamous cell carcinoma (VV-SCC) has received little attention. A total of 182 women with invasive VV-SCC (116 with VV-SCC(vulva), 66 with VV-SCC(vagina)), 164 uterine corpus cancer controls and 518 population controls were interviewed in a population-based case-control study in Denmark, and 87 (48%) of the VV-SCC cases had tissue samples examined for human papillomavirus (HPV) DNA using the GP5+/6+ PCR-EIA assay and subsequent reverse line blotting for HPV typing. Logistic regression-derived odds ratios with 95% confidence intervals served as relative risks. Cervical cancer-associated high-risk HPVs (hrHPVs) were detectable in most (89%) examined cases of VV-SCC(vagina) and in half (50%) of cases of VV-SCC(vulva) ($p < 0.001$). In site-specific multivariate logistic regression analyses, statistically significant risk factors for both VV-SCC(vulva) and VV-SCC(vagina) included measures of hrHPV exposure (anogenital warts for VV-SCC(vulva); cervical neoplasia and poor genital hygiene for VV-SCC(vagina)), tobacco smoking and alcohol consumption. Furthermore, socioeconomic variables (marital status and years at school) were associated with risk of VV-SCC(vulva). Comparing hrHPV-positive and hrHPV-negative VV-SCCs in polytomous logistic regression analysis revealed that tobacco smoking and cervical neoplasia were significant risk factors only for hrHPV-positive VV-SCCs. Our study shows that VV-SCC(vulva) and VV-SCC(vagina) share measures of prior hrHPV exposure, tobacco smoking and alcohol consumption as statistically significant risk factors. HPV vaccination programs aimed at reducing the burden of cervical cancers are likely to also provide considerable protection against VV-SCCs.

Mortensen, G. L. and H. K. Larsen (2010). "The quality of life of patients with genital warts: a qualitative study." BMC Public Health **10**: 113.

BACKGROUND: Genital warts, which are caused by infection with human papillomavirus (HPV), are one of the most common sexually transmitted diseases in Europe. Although genital warts are commonly perceived as a non-serious condition, treatment is often long, of varying effectiveness and the recurrence rate is high. Very few studies have been performed on the personal consequences of genital warts. The aim of this qualitative study, set in Denmark, was to examine the ways in which genital warts may affect patients' quality of life. METHODS: To obtain an in-depth understanding of patients' perceptions of genital warts, we used qualitative focus-group interviews with five men and five women aged between 18 and 30 years who had genital warts. The interview guide was based on a literature review that identified important issues and questions. The data were analysed using a medical anthropological approach. RESULTS: Patients' experiences were related to cultural conceptions of venereal diseases and the respective identities and sexuality of the sexes. The disease had negative psychological and social effects both for men and for women and it affected their sex and love lives, in particular. The psychological burden of the disease was increased by the uncertain timeline and the varying effectiveness of treatment. We identified a need for more patient information about the disease and its psycho-sexual aspects. CONCLUSIONS: The men and women participating in this study considered

their quality of life to be significantly lowered because of genital warts. The experiences described by the participants give insights that may be valuable in treatment and counselling.The quadrivalent HPV vaccine that has now been added to the childhood vaccination programme for girls in Denmark for the prevention of cervical cancer can also prevent 90% of cases of genital warts. Our results suggest that HPV vaccination could considerably reduce the largely unacknowledged psychological and social burden associated with genital warts, in men as well as women.

Nielsen, A., T. Iftner, C. Munk and S. K. Kjaer (2009). "Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women." Sex Transm Dis **36**(10): 609-615.

BACKGROUND: Human papillomavirus (HPV) is the cause of cervical cancer. To better understand the natural history of HPV, we assessed the incidence of type-specific HPV infection and examined risk factors for acquisition of high-risk (HR) HPV infection in Danish women. METHODS: A population-based prospective cohort study of women aged 20 to 29 years was conducted. Participants were interviewed and underwent 2 gynaecological examinations 2 years apart. Women for whom Hybrid Capture 2 results were available at both visits were included in the analysis (n = 7454). RESULTS: A HR HPV infection was acquired by 12.8% of the women during follow-up. The incidence decreased with increasing age. The commonest types were HPV16, HPV31, and HPV52. HPV66, HPV58, and HPV53 were mainly acquired with other HR types. Multiple HR types were acquired in 50% of the women who became HPV-positive during follow-up. In initially HPV-negative women age, number of sexual partners, and oral contraceptive use were the main risk factors for acquisition, particularly of multiple HR HPV types. CONCLUSIONS: HPV infections were commonly acquired. We confirmed the sexually transmitted nature of the infection. Our findings show that both the level of potential exposure and other behavioral factors increase the risk for HR HPV acquisition.

Nielsen, A., T. Iftner, M. Norgaard, C. Munk, J. Junge and S. K. Kjaer (2012). "The importance of low-risk HPV infection for the risk of abnormal cervical cytology/histology in more than 40 000 Danish women." Sex Transm Infect **88**(8): 627-632.

OBJECTIVES: To estimate the age and type-specific distribution of low-risk (LR) human papillomavirus (HPV) types in cervical samples from women in the general population and to assess the distribution of LR-HPV without the coexistence of high-risk HPV types in different cytology and histology categories. METHODS: In a cross-sectional study, liquid-based cytology samples (SurePath) were collected over a 3-year period. The samples were HPV tested by Hybrid Capture II (HC2; Digene) and genotyped using a PCR-based assay (INNO-LiPAv2; Innogenetics Inc.). A total of 40 382 women (14-95 years of age) were included in the study. By linkage with the nationwide Pathology Data Bank, the HPV test results were directly linked to cytological diagnoses made from the same samples and to subsequent histology results. RESULTS: Overall, 2790 women (6.9%) tested positive for LR-HPV types, with HPV6 and HPV70 being the most frequent types detected, whereas HPV11 was uncommon. The highest prevalence was observed in the youngest age group (</=19 years). The LR-HPV prevalence was 6.3% in women with normal cytology, 33.1% in atypical squamous cells of undetermined significance (ASCUS), 19.6% in low-grade squamous intraepithelial lesion and 12.7% in those with high-grade squamous intraepithelial lesion. When considering women with LR-HPV alone, the prevalence was 2.0% (normal cytology), 11.3% (ASCUS), 2.6% (low-grade squamous intraepithelial lesion) and 0.7% in women with high-grade squamous intraepithelial lesion, respectively. A similar pattern was observed in relation to the histological diagnoses with the majority of LR-HPV infections detected in CIN1 lesions (24.7%). CONCLUSIONS: LR-HPV types alone are relatively common in ASCUS, whereas LR-HPV types without coexisting high-risk HPV types are virtually never detected in severe cervical lesions.

Nielsen, A., S. K. Kjaer, C. Munk and T. Iftner (2008). "Type-specific HPV infection and multiple HPV types: prevalence and risk factor profile in nearly 12,000 younger and older Danish women." Sex Transm Dis **35**(3): 276-282.

OBJECTIVES: Human papillomavirus (HPV) is considered a necessary cause of cervical cancer. The aim of the current study was to determine the burden of HPV infection among randomly sampled Danish women before the vaccine against HPV is implemented. Further we assessed the risk factor profile for prevalent high risk (HR) HPV infection and infection with multiple HR HPV types. METHODS: In the present cross-sectional study, we used baseline data from a population-based cohort study where participants were interviewed and had a gynecological examination. Cervical samples were analyzed for HR HPV using Hybrid capture 2 in 10,544 women aged 20-29 years and 1443 women aged 40-50 years. Genotyping was performed using LiPA. RESULTS: The prevalence of HR HPV was 17.9% and 4.4% in women aged 20-29 years and 40-50 years, respectively. HPV16 was the most common HR type overall and among women with abnormal cytology. Multiple HPV types were highly prevalent, notably in the younger cohort. Lifetime number of sexual partners was the main risk factor for HR HPV infection (adj. OR = 2.8 and OR = 3.4 for > or =15 partners vs. < or =4 in respectively younger and older women), whereas number of recent sexual partners was only associated with risk in younger women. Number of partners, oral contraceptive use and self-reported chlamydia infection increased the risk of having multiple HR HPV types (compared to having a single HR HPV type). CONCLUSIONS: HR HPV infection was common among younger women, with HPV16 as the predominant type. We confirmed the importance of sexual activity for the risk of HR HPV infection. In addition, we found that sexual behavior also play an important role for the risk of having multiple HR HPV types.

Nielsen, A., S. K. Kjaer, C. Munk, M. Osler and T. Iftner (2010). "Persistence of high-risk human papillomavirus infection in a population-based cohort of Danish women." J Med Virol **82**(4): 616-623.

Persisting human papillomavirus (HPV) infection is a critical step in cervical carcinogenesis. This study was conducted to determine the type-specific HPV persistence and risk factors for persistence of high-risk HPV infections in a large cohort of Danish women. The study was based on a population-based prospective cohort study of women aged 20-29 years. Participants were interviewed and underwent two gynecological examinations 2 years apart. Women with Hybrid Capture 2 results at enrolment and a follow-up visit were included in the analysis (n = 7,418). Persistence was defined as positivity for the same high-risk HPV type at both examinations. Overall, 4.2% of the women had persistent HPV infection, accounting for 26.9% of the initially HPV-positive women. HPV 16, HPV 58, and HPV 31, all from species group alpha 9, were the most persistent types; however, other high-risk HPV types that are detected rarely in cancer cases were also likely to persist. The number of high-risk HPV types and detection of HPV 16 infection at baseline and ever use of oral contraceptives increased the risk for persistence. The risk factor analyses also showed that use of an intrauterine device decreased the risk for persistent high-risk HPV infection among women with one high-risk HPV type at baseline. No association was found with viral load or smoking. In conclusion, persistent high-risk HPV infection, especially HPV 16 persistence, was common among women positive for high-risk HPV.

Nielsen, A., C. Munk, H. O. Jorgensen, J. F. Winther, A. J. van den Brule and S. K. Kjaer (2013). "Multiple-type human papillomavirus infection in younger uncircumcised men." Int J STD AIDS **24**(2): 128-133.

A cohort of 388 young men enrolled for military service in the Danish army was established and the participants underwent a clinical examination with human papillomavirus (HPV) testing. In addition, a questionnaire containing questions regarding sociodemographic variables, sexual habits and lifestyle factors was completed. The prevalence of HPV was 33.4% in this cohort of uncircumcised men aged 18-29 years. Multiple HPV types were prevalent with one-third of the HPV-positive men being positive for more than one HPV type. Number of recent sexual partners and infrequent condom use were strong risk

factors, particularly in men having multiple HPV types. Our findings re-emphasize the importance of sexual transmission and also point to a role of factors that may be related to individual susceptibility as genital warts, alcohol intake and, to a lesser extent, smoking were strongly associated with having multiple HPV types.

Nielsen, A., C. Munk and S. K. Kjaer (2012). "Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008." Int J Cancer **130**(5): 1168-1173.

The aim of the study was to determine the incidences of anal cancer and high-grade anal intraepithelial neoplasia (AIN2/3) over time in Danish women and men. Describing the burden of anal cancer and AIN may be valuable in future evaluations of the human papillomavirus (HPV) vaccine. We included all anal cancers in the Danish Cancer Register in the period 1978-2008 and all cases of AIN2/3 in the Danish Registry of Pathology. Overall and age-, period- and histology-specific incidence rates were estimated. During the 30-year period, 2,187 anal cancers were identified, two thirds of which were in women. Between 1978-1982 and 2003-2008, the age-standardized incidence rate of anal cancer increased from 0.68 to 1.48 per 100,000 person-years in women and from 0.45 to 0.80 per 100,000 person-years in men. Although there is no systematic screening for AIN in Denmark, we nevertheless identified 608 cases of AIN2/3 during the study period. The average annual percentage change of 5% between 1998 and 2008 represents a steep increase in the incidence of AIN in both genders. Furthermore, the incidence rate of HPV-associated anal cancers increased significantly, whereas that of non-HPV-associated histological types levelled out or even declined during the 30 years of observation. In women, the increase in HPV-associated cancers was more pronounced among those under 60 years of age. Our findings indicate that vaccines against HPV might play an important role in the prevention of anal cancer and its precursor lesions.

Nygard, M., B. T. Hansen, J. Dillner, C. Munk, K. Oddsson, L. Tryggvadottir, M. Hortlund, K. L. Liaw, E. J. Dasbach and S. K. Kjaer (2014). "Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance." PLoS One **9**(2): e88323.

Olsen, J., T. R. Jorgensen, K. Kofoed and H. K. Larsen (2012). "Incidence and cost of anal, penile, vaginal and vulvar cancer in Denmark." BMC Public Health **12**: 1082.

BACKGROUND: Besides being a causative agent for genital warts and cervical cancer, human papillomavirus (HPV) contributes to 40-85% of cases of anal, penile, vaginal and vulvar cancer and precancerous lesions. HPV types 16 & 18 in particular contribute to 74-93% of these cases. Overall the number of new cases of these four cancers may be relatively high implying notable health care cost to society. The aim of this study was to estimate the incidence and the health care sector costs of anal, penile, vaginal and vulvar cancer. METHODS: New anogenital cancer patients were identified from the Danish National Cancer Register using ICD-10 diagnosis codes. Resource use in the health care sector was estimated for the year prior to diagnosis, and for the first, second and third years after diagnosis. Hospital resource use was defined in terms of registered hospital contacts, using DRG (Diagnosis Related Groups) and DAGS (Danish Outpatient Groups System) charges as cost estimates for inpatient and outpatient contacts, respectively. Health care consumption by cancer patients diagnosed in 2004-2007 was compared with that by an age- and sex-matched cohort without cancer. Hospital costs attributable to four anogenital cancers were estimated using regression analysis. RESULTS: The annual incidence of anal cancer in Denmark is 1.9 per 100,000 persons. The corresponding incidence rates for penile, vaginal and vulvar cancer are 1.7, 0.9 and 3.6 per 100,000 males/females, respectively. The total number of new cases of these four cancers in Denmark is about 270 per year. In comparison, the total number of new cases cervical cancer is around 390 per year. The total cost of anogenital cancer to the hospital sector was

estimated to be 7.6 million Euros per year. Costs associated with anal and vulvar cancer constituted the majority of the costs. CONCLUSIONS: Anogenital cancer incurs considerable costs to the Danish hospital sector. It is expected that the current HPV vaccination program will markedly reduce this burden.

Rebolj, M., E. Lynge and J. Bonde (2011). "Human papillomavirus testing and genotyping in cervical screening." Expert Rev Anticancer Ther **11**(7): 1023-1031.

Mass vaccination against human papillomavirus (HPV) genotypes 16 and 18 will, in the long term, reduce the incidence of cervical cancer, but screening will remain an important cancer control measure in both vaccinated and unvaccinated women. Since the 1960s, cytology screening has helped to reduce the incidence of cervical cancer, but has a low sensitivity for high-grade cervical intraepithelial neoplasia (CIN) and requires frequent testing. Several HPV tests have become available commercially. They appear to be more sensitive for high-grade CIN, and may further reduce the incidence of cervical cancer compared with cytology. However, they are associated with an increased frequency of positive tests without underlying CIN, and therefore increase the need for colposcopy and repeated testing. This problem will pose a major challenge for switching from cytology-based to HPV-based screening. The aim of this article is to discuss the role and the use of HPV tests and HPV genotyping in unvaccinated women.

Rebolj, M., S. Preisler, D. M. Ejegod, J. Bonde, C. Rygaard and E. Lynge (2013). "Prevalence of Human Papillomavirus infection in unselected SurePath samples using the APTIMA HPV mRNA assay." J Mol Diagn **15**(5): 670-677.

The APTIMA Human Papillomavirus (HPV) Assay detects E6/E7 mRNA from 14 human papillomavirus genotypes. Horizon was a population-based split-sample study among well-screened women, with an aim to compare APTIMA, Hybrid Capture 2 (HC2), and liquid-based cytology (LBC) using SurePath samples. APTIMA testing on the PANTHER platform, and HC2 testing on the Rapid Capture System were performed in accordance with protocols agreed on with the manufacturers before the study, on 5070 consecutive, routine, cervical cytology samples from Copenhagen, Denmark. In this high-risk population, 17% of all samples tested positive on APTIMA, 20% of samples tested positive on HC2, and 7% of samples had abnormal cytology. Among the 4411 samples without recent abnormalities, 15% tested positive on APTIMA, 19% tested positive on HC2, and 5% had abnormal cytology. The kappa coefficient of 0.75 suggested substantial agreement between APTIMA and HC2. This is the first APTIMA study using SurePath samples on the PANTHER platform. The trends in positivity rates on SurePath samples for APTIMA, HC2, and LBC were consistent with studies based on PreservCyt samples, and the agreement between the two HPV assays was substantial. The high proportions of women testing positive suggest that in countries with a high HPV prevalence, caution will be needed if HPV tests, including mRNA-based tests, are to replace LBC.

Rusan, M., T. E. Klug, J. J. Henriksen, J. H. Bonde, K. Fuursted and T. Ovesen (2015). "Prevalence of tonsillar human papillomavirus infections in Denmark." Eur Arch Otorhinolaryngol **272**(9): 2505-2512.

The incidence of tonsillar carcinomas associated with Human Papillomavirus (HPV) infection has increased dramatically over the last three decades. In fact, currently in Scandinavia, HPV-associated cases account for over 80 % of tonsillar carcinoma cases. Yet, the epidemiology and natural history of tonsillar HPV infections remains poorly characterized. Our aim was to characterize such infections in the Danish population in tumor-free tonsillar tissue. Unlike previous studies, we considered both palatine tonsils. We examined both tonsils from 80 patients with peritonsillar abscess (n = 25) or chronic tonsillar disease (n = 55). HPV was detected by nested PCR with PGMY 09/11 and GP5+/GP6+L1 consensus primers, and typed by sequencing. Samples were also analyzed using a higher-throughput method, the CLART HPV 2 Clinical Array Assay. The overall prevalence of HPV tonsillar infection was 1.25 % (1/80, 95 % CI 0.03-6.77 %) by nested PCR, and 0 % by CLART HPV2 Clinical Array. The HPV-positive patient was a 16-year-old female

with recurrent tonsillitis and tonsillar hypertrophy. The type detected was HPV6. HPV was not detected in the contralateral tonsil of this patient. Compared to cervical HPV infections in Denmark, tonsillar HPV infections are 10- to 15-fold less frequent. In the HPV-positive patient in this study, HPV was detected in only one of the tonsils. This raises the possibility that prior studies may underestimate the prevalence of HPV infections, as they do not consider both palatine tonsils.

Schmidt, S. A., S. J. Hamilton-Dutoit, D. K. Farkas, T. Steiniche and H. T. Sorensen (2015). "Human papillomavirus and the incidence of nonmelanoma and melanoma skin cancer using cervical conization as a surrogate marker: a nationwide population-based Danish cohort study." Ann Epidemiol **25**(4): 293-296.e292.

PURPOSE: Human papillomavirus' (HPV's) role in skin cancer is controversial. To examine whether an individual is prone to develop a chronic oncogenic infection, we conducted a nationwide population-based cohort study of the risk of skin cancer after another HPV-related neoplasia-that is, cervical high-grade dysplasia or carcinoma-using cervical conization as a surrogate marker. METHODS: Using Danish registries, we identified all women who underwent conization from 1978 to 2011 (n = 87,164) and followed them until first-time skin cancer diagnosis, death, emigration, or 31 December 2011, whichever came first. We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM) according to national incidence rates. RESULTS: The 1-year absolute risks were 0.0012%, 0.045%, and 0.029% for SCC, BCC, and MM, respectively. Conization was clearly associated with increased incidence of SCC (SIR = 1.37; 95% CI: 1.13-1.65), but not MM (SIR = 1.00; 95% CI: 0.91-1.11). BCC risk was slightly increased (SIR = 1.08; 95% CI: 1.02-1.13). CONCLUSIONS: The association between conization and cutaneous SCC provides evidence for conization as a marker of underlying general susceptibility to oncogenic HPV.

Skaaby, S. and K. Kofoed (2011). "Anogenital warts in Danish men who have sex with men." Int J STD AIDS **22**(4): 214-217.

To determine the prevalence of anogenital warts (AGWs) and concurrent sexually transmitted infections (STIs) in men who have sex with men (MSM), and their knowledge of human papillomavirus (HPV). Attitudes towards the HPV vaccine among MSM are explored. A web-based cross-sectional survey on AGWs, sociodemographic factors and sexual behaviour conducted in August 2009 in Denmark. Overall 25.2% of the 1184 respondents reported a prior or current episode of AGWs. The prevalence of AGW was significantly higher in homosexuals compared with bisexuals, in men with high levels of education and in those with a high number of sexual partners within the last year. MSM with a history of another STI reported a significantly higher prevalence of warts. More than 70% did not know what causes AGWs. If a free HPV vaccine were to be offered, 94.4% would like to receive it. These data suggest a high prevalence of AGWs in Danish MSM. The awareness of HPV is low; however, the acceptance of a HPV vaccine seems high.

Thomsen, L. T., K. Frederiksen, C. Munk, J. Junge, P. E. Castle, T. Iftner and S. K. Kjaer (2014). "High-risk and low-risk human papillomavirus and the absolute risk of cervical intraepithelial neoplasia or cancer." Obstet Gynecol **123**(1): 57-64.

OBJECTIVE: To determine the absolute risk of cervical intraepithelial neoplasia (CIN) grade 3 or cervical cancer (CIN 3 or worse) after detection of low-risk human papillomavirus (HPV) and after a negative high-risk HPV test. METHODS: In this prospective cohort study, consecutive liquid-based cervical cytology samples were collected from women screened for cervical cancer in Copenhagen, Denmark, during 2002-2005. Samples were tested with a clinical test for 13 high-risk and five low-risk HPV types. The cohort (N=35,539; aged 14-90 years) was monitored in a nationwide pathology register for up to 10.5 years for development of CIN 3 or worse. RESULTS: The 8-year absolute risk of CIN 3 or worse was 1.1%

(95% confidence interval [CI] 1.0-1.3%) for HPV-negative women; 1.7% (0.8-2.6%) for low-risk HPV-positive women without concurrent high-risk HPV; 17.4% (16.4-18.5%) for high-risk HPV-positive women without concurrent low-risk HPV; and 15.9% (13.5-18.3%) for women with concurrent high-risk and low-risk HPV. The 8-year absolute risk of CIN 3 or worse after a negative high-risk HPV test (irrespective of low-risk HPV status) was lower than after a normal cytology result among women aged younger than 30 years (3.5% [95% CI, 2.9-4.0%] compared with 6.9% [6.2-7.5%], P<.001) and women aged 30 years or older (0.7% [95% CI, 0.6-0.9%] compared with 1.8% [95% CI, 1.6-2.0%], P<.001). CONCLUSION: A negative high-risk HPV test provides greater long-term reassurance against CIN 3 or worse than normal cytology. Detection of low-risk HPV does not predict CIN 3 or worse. Cervical cancer screening should not include testing for low-risk HPV types. LEVEL OF EVIDENCE: II.

Brinth, L., A. C. Theibel, K. Pors and J. Mehlsen (2015). "Suspected side effects to the quadrivalent human papilloma vaccine." Dan Med J **62**(4): A5064.

INTRODUCTION: The quadrivalent vaccine that protects against human papilloma virus types 6, 11, 16 and 18 (Q-HPV vaccine, Gardasil) was included into the Danish childhood vaccination programme in 2009. During the past years, a collection of symptoms primarily consistent with sympathetic nervous system dysfunction have been described as suspected side effects to the Q-HPV vaccine. METHODS: We present a description of suspected side effects to the Q-HPV vaccine in 53 patients referred to our Syncope Unit for tilt table test and evaluation of autonomic nervous system function. RESULTS: All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character. CONCLUSION: We found consistency in the reported symptoms as well as between our findings and those described by others. Our findings neither confirm nor dismiss a causal link to the Q-HPV vaccine, but they suggest that further research is urgently warranted to clarify the pathophysiology behind the symptoms experienced in these patients and to evaluate the possibility and the nature of any causal link and hopefully establish targeted treatment options. FUNDING: not relevant. TRIAL REGISTRATION: not relevant.

Callreus, T., H. Svanstrom, N. M. Nielsen, S. Poulsen, P. Valentiner-Branth and A. Hviid (2009). "Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events." Vaccine **27**(22): 2954-2958.

Determining incidence rates of potential adverse events before and after an immunisation programme is initiated, provides a useful framework for the evaluation of vaccine safety concerns. Human papillomavirus vaccination (HPV) of adolescent girls has recently been introduced in Denmark. Using a nationwide hospitalisation registry we estimated incidence rates of immune-mediated disorders before HPV vaccination in a cohort of 418,289 Danish girls aged 12-15 years. We further estimated the expected number of cases of immune-mediated disorders occurring in temporal relationship to a hypothetical HPV vaccination schedule purely by chance. Our results and analytical approach provides a framework for the evaluation of adverse event reports following immunisation of adolescent girls.

Chandler, R. E., K. Juhlin, J. Fransson, O. Caster, I. R. Edwards and G. N. Noren (2016). "Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster Analysis of Reports in VigiBase(R)." Drug Saf.

INTRODUCTION: A number of safety signals-complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and chronic fatigue syndrome (CFS)-have emerged with human papillomavirus (HPV) vaccines, which share a similar pattern of symptomatology. Previous signal evaluations and epidemiological studies have largely relied on traditional methodologies and signals have been considered individually. OBJECTIVE: The aim of this study was to explore global reporting patterns for HPV vaccine for subgroups of reports with similar adverse event (AE) profiles. METHODS: All individual

case safety reports (reports) for HPV vaccines in VigiBase(R) until 1 January 2015 were identified. A statistical cluster analysis algorithm was used to identify natural groupings based on AE profiles in a data-driven exploratory analysis. Clinical assessment of the clusters was performed to identify clusters relevant to current safety concerns. RESULTS: Overall, 54 clusters containing at least five reports were identified. The four largest clusters included 71 % of the analysed HPV reports and described AEs included in the product label. Four smaller clusters were identified to include case reports relevant to ongoing safety concerns (total of 694 cases). In all four of these clusters, the most commonly reported AE terms were headache and dizziness and fatigue or syncope; three of these four AE terms were reported in >50 % of the reports included in the clusters. These clusters had a higher proportion of serious cases compared with HPV reports overall (44-89 % in the clusters compared with 24 %). Furthermore, only a minority of reports included in these clusters included AE terms of diagnoses to explain these symptoms. Using proportional reporting ratios, the combination of headache and dizziness with either fatigue or syncope was found to be more commonly reported in HPV vaccine reports compared with non-HPV vaccine reports for females aged 9-25 years. This disproportionality remained when results were stratified by age and when those countries reporting the signals of CRPS (Japan) and POTS (Denmark) were excluded. CONCLUSIONS: Cluster analysis reveals additional reports of AEs following HPV vaccination that are serious in nature and describe symptoms that overlap those reported in cases from the recent safety signals (POTS, CRPS, and CFS), but which do not report explicit diagnoses. While the causal association between HPV vaccination and these AEs remains uncertain, more extensive analyses of spontaneous reports can better identify the relevant case series for thorough signal evaluation.

Ferris, D., R. Samakoses, S. L. Block, E. Lazcano-Ponce, J. A. Restrepo, K. S. Reisinger, J. Mehlsen, A. Chatterjee, O. E. Iversen, H. L. Sings, Q. Shou, T. A. Sausser and A. Saah (2014). "Long-term study of a quadrivalent human papillomavirus vaccine." Pediatrics **134**(3): e657-665.

BACKGROUND: We present a long-term safety, immunogenicity, and effectiveness study of a quadrivalent human papillomavirus (HPV4) vaccine. METHODS: Sexually naive boys and girls aged 9 to 15 years (N = 1781) were assigned (2:1) to receive HPV4 vaccine or saline placebo at day 1 and months 2 and 6. At month 30, the placebo group (n = 482) received HPV4 vaccine following the same regimen and both cohorts were followed through month 96. Subjects >/= 16 years were eligible for effectiveness evaluations. The primary objective was to evaluate the long-term anti-HPV6/11/16/18 serological levels. The secondary objective was to estimate vaccine effectiveness against HPV6/11/16/18-related persistent infection or disease. RESULTS: For each of the HPV4 vaccine types, vaccination-induced anti-HPV response persisted through month 96. Among 429 subjects who received HPV4 vaccine at a mean age of 12, none developed HPV6/11/16/18-related disease or persistent infection of >/= 12 months' duration. Acquisition of new sexual partners (among those >/= 16 years) was approximately 1 per year. Subjects receiving HPV4 vaccine at month 30 (mean age 15 years) had a similar baseline rate of seropositivity to >/= 1 of the 4 HPV types to those vaccinated at day 1 (mean age 12 years; 1.9% [9 of 474] vs 1.7% [20 of 1157]); however, 4 of the 9 subjects vaccinated at the later age were seropositive to 3 vaccine types, indicating previous HPV exposure. No new significant serious adverse events were observed for 8 years postvaccination in both genders. CONCLUSIONS: When administered to adolescents, the HPV4 vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years.

Hammer, A., L. K. Petersen, N. Rolving, M. F. Boxill, K. H. Kallesoe, S. Becker, U. Fredberg, V. N. Sorensen, C. U. Rask, P. K. Fink and J. Blaakaer (2016). "[Possible side effects from HPV vaccination in Denmark]." Ugeskr Laeger **178**(26).

HPV vaccination offers protection against ~70% of cervical cancers, however, serious concerns have been raised about the possible side effects from HPV vaccination. Studies have found no increased risk of neurologic disease, autoimmune disorder, thromboembolic disease, postural orthostatic

tachycardia syndrome, or complex regional pain syndrome in HPV-vaccinated persons compared to unvaccinated persons. Affected individuals should undergo a proper clinical examination to ensure a correct diagnosis and treatment, because symptoms might arise due to a somatic, psychiatric or functional disorder.

Larson, H. J., R. Wilson, S. Hanley, A. Parys and P. Paterson (2014). "Tracking the global spread of vaccine sentiments: the global response to Japan's suspension of its HPV vaccine recommendation." Hum Vaccin Immunother **10**(9): 2543-2550.

In June 2013 the Japanese Ministry of Health, Labor, and Welfare (MHLW) suspended its HPV vaccination recommendation after a series of highly publicized alleged adverse events following immunization stoked public doubts about the vaccine's safety. This paper examines the global spread of the news of Japan's HPV vaccine suspension through online media, and takes a retrospective look at non-Japanese media sources that were used to support those claiming HPV vaccine injury in Japan. METHODS: Two searches were conducted. One searched relevant content in an archive of Google Alerts on vaccines and vaccine preventable diseases. The second search was conducted using Google Search on January 6th 2014 and on July 18th 2014, using the keywords, "HPV vaccine Japan" and "cervical cancer vaccine Japan." Both searches were used as Google Searches render more (and some different) results than Google Alerts. RESULTS: Online media collected and analyzed totalled 57. Sixty 3 percent were published in the USA, 23% in Japan, 5% in the UK, 2% in France, 2% in Switzerland, 2% in the Philippines, 2% in Kenya and 2% in Denmark. The majority took a negative view of the HPV vaccine, the primary concern being vaccine safety. DISCUSSION: The news of Japan's suspension of the HPV vaccine recommendation has traveled globally through online media and social media networks, being applauded by anti-vaccination groups but not by the global scientific community. The longer the uncertainty around the Japanese HPV vaccine recommendation persists, the further the public concerns are likely to travel.

Scheller, N. M., H. Svanstrom, B. Pasternak, L. Arnheim-Dahlstrom, K. Sundstrom, K. Fink and A. Hviid (2015). "Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system." Jama **313**(1): 54-61.

IMPORTANCE: Case reports have suggested a link between human papillomavirus (HPV) vaccination and development of multiple sclerosis and other demyelinating diseases. OBJECTIVE: To investigate if quadrivalent HPV (qHPV) vaccination is associated with an increased risk of multiple sclerosis and other demyelinating diseases. DESIGN, SETTING, AND PARTICIPANTS: Using nationwide registers we identified a cohort of all females aged 10 years to 44 years in Denmark and Sweden, followed up from 2006 to 2013, information on qHPV vaccination, and data on incident diagnoses of multiple sclerosis and other demyelinating diseases. The primary analysis used a cohort design including vaccinated and unvaccinated study participants. A secondary analysis used a self-controlled case-series design including only cases. Both analyses used a 2-year risk period following vaccination. EXPOSURES: Information on qHPV vaccination was obtained through the national vaccination and prescription registers. MAIN OUTCOMES AND MEASURES: The primary outcomes were multiple sclerosis and a composite end point of other demyelinating diseases. Incidence rate ratios were estimated using Poisson regression, comparing rates of events in the 2-year risk periods following vaccination and in unvaccinated time periods. RESULTS: The study included 3,983,824 females, among whom 789,082 received a total of 1,927,581 qHPV vaccine doses. During follow-up, 4322 multiple sclerosis cases and 3300 cases of other demyelinating diseases were identified, of which 73 and 90, respectively, occurred within the risk period. In the cohort analysis, there was no increased risk of multiple sclerosis (crude incidence rates, 6.12 events/100,000 person-years [95% CI, 4.86-7.69] and 21.54 events/100,000 person-years [95% CI, 20.90-22.20] for the vaccinated and unvaccinated periods; adjusted rate ratio, 0.90 [95% CI, 0.70-1.15]) or other demyelinating diseases (crude incidence rates, 7.54 events/100,000 person-years [95% CI, 6.13-9.27] and

16.14 events/100,000 person-years [95% CI, 15.58-16.71]; adjusted rate ratio, 1.00 [95% CI, 0.80-1.26]) associated with qHPV vaccination. Similarly, no increased risk was found using the self-controlled case-series design (multiple sclerosis: incidence ratio, 1.05 [95% CI, 0.79-1.38]; other demyelinating diseases: incidence ratio, 1.14 [95% CI, 0.88-1.47]). CONCLUSIONS AND RELEVANCE: In this study with nationwide coverage of 2 Scandinavian countries, qHPV vaccination was not associated with the development of multiple sclerosis or other demyelinating diseases. These findings do not support concerns about a causal relationship between qHPV vaccination and demyelinating diseases.

Session 4 Prevention and control of HPV in Denmark

HPV vaccination programmes in Denmark
Palle Valentiner-Branth

Cervical cancer screening programmes in Denmark
Elsebeth Lynge
References provided by the speaker:

Dansk Kvalitetsdatabase for Livmoderhalskræftscreening. Årsrapport 2015.
https://www.sundhed.dk/content/cms/82/4682_dkls-%C3%A5rsrapport-2015.pdf

Home sampling for hrHPV testing in Central Denmark Region
Berit Andersen
References provided by the speaker:

Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M (2015). "Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials." Eur J Cancer **51**(16): 2375-85. doi: 10.1016/j.ejca.2015.07.006.

INTRODUCTION: Population coverage for cervical cancer screening is an important determinant explaining differences in the incidence of cervical cancer between countries. Offering devices for self-sampling has the potential to increase participation of hard-to-reach women. METHODS: A systematic review and meta-analysis were performed to evaluate the participation after an invitation including a self-sampling device (self-sampling arm) versus an invitation to have a sample taken by a health professional (control arm), sent to under-screened women. RESULTS: Sixteen randomised studies were found eligible. In an intention-to-treat analysis, the pooled participation in the self-sampling arm was 23.6% (95% confidence interval (CI)=20.2-27.3%), when self-sampling kits were sent by mail to all women, versus 10.3% (95% CI=6.2-15.2%) in the control arm (participation difference: 12.6% [95% CI=9.3-15.9]). When women had to opt-in to receive the self-sampling device, as used in three studies, the pooled participation was not higher in the self-sampling compared to the control arm (participation difference: 0.2% [95% CI=-4.5-4.9%]). CONCLUSION: An increased participation was observed in the self-sampling arm compared to the control arm, if self-sampling kits were sent directly to women at their home address. However, the size of the effect varied substantially among studies. Since participation was similar in both arms when women had to opt-in, future studies are warranted to discern opt-in scenarios that are most acceptable to women.

Arbyn M, Castle PE (2015). "Offering Self-Sampling Kits for HPV Testing to Reach Women Who Do Not Attend in the Regular Cervical Cancer Screening Program." Cancer Epidemiol Biomarkers Prev **24**(5):769-72, doi: 10.1158/1055-9965.EPI-14-1417.

In 2016, the Netherlands will switch, as first European country, from cytology-based to HPV-based cervical cancer screening, with cytology triage for those with a positive HPV test. The new Dutch program includes sending self-sampling devices to women who do not respond to an invitation to have a cervical sample taken by their general practitioner. The cost-effectiveness of this additional strategy will depend on its capacity to recruit nonscreened women and in particular those at increased risk of cervical (pre)cancer, the possible switch of previous responders to self-sampling, the accuracy and cost of the HPV

assay-self-sampler combination, and the compliance of women being self-sample HPV-positive with further follow-up. Validated PCR-based assays, detecting high-risk HPV DNA, are as accurate on self-samples as on clinician-collected samples. On the contrary, HPV assays, based on signal amplification, are less sensitive and specific on self-samples. The introduction of self-sampling strategies should be carefully prepared and evaluated in pilot studies integrated in well-organized settings before general rollout. Opt-in procedures involving a request for a self-sampler may reduce response rates. Therefore, an affordable device that can be included with the invitation to all nonattendees may yield a stronger effect on participation.

Kristensson, J. H., B. B. Sander, M. von Euler-Chelpin and E. Lynge (2014). "Predictors of non-participation in cervical screening in Denmark." Cancer Epidemiol **38**(2): 174-180.

PURPOSE: The aims of this study were to identify demographic and socio-economic predictors of non-participation in cervical screening in Denmark, and to evaluate the influence of health care use on screening participation. METHODS: A population based register study was undertaken using data from the Central Population Register, the national Patobank, and Statistics Denmark. The study included women aged 25-54 years on 1st of January 2002, living in Denmark during the next 5 years, and without a history of total hysterectomy, N=1,052,447. Independent variables included age, civil status, nationality, level of education, and use of health care. Associations with non-participation in screening were determined with logistic regression. RESULTS: Main predictors of non-participation were limited or no contact with dental services (odds ratio (OR)=2.36), general practitioners (OR=1.75), and high age (OR=1.98). Other important factors for non-participation were primary school education only (OR=1.53), not being married (OR=1.49), and foreign nationality (OR=1.32). CONCLUSION: A 2-1.5-fold difference in non-participation in cervical screening in Denmark was found across various population sub-groups. Increased screening compliance among women with primary school education only, and limited or no use of primary health care services in general could potentially diminish the current social inequalities in cervical cancer incidence, and thus decrease the overall high incidence of this disease in Denmark.

Tranberg, M., B. H. Bech, J. Blaakaer, J. S. Jensen, H. Svanholm and B. Andersen (2016). "Study protocol of the CHOiCE trial: a three-armed, randomized, controlled trial of home-based HPV self-sampling for non-participants in an organized cervical cancer screening program." BMC Cancer **16**(1): 835.

BACKGROUND: The effectiveness of cervical cancer screening programs is challenged by suboptimal participation and coverage. Offering cervico-vaginal self-sampling for human papillomavirus testing (HPV self-sampling) to non-participants can increase screening participation. However, the effect varies substantially among studies, especially depending on the approach used to offer HPV self-sampling. The present trial evaluates the effect on participation in an organized screening program of a HPV self-sampling kit mailed directly to the home of the woman or mailed to the woman's home on demand only, compared with the standard second reminder for regular screening. METHODS/DESIGN: The CHOiCE trial is a parallel, randomized, controlled, open-label trial. It will include 9327 women aged 30-64 years who are living in the Central Denmark Region and who have not participated in cervical cancer screening after an invitation and one reminder. The women will be equally randomized into three arms: 1) Directly mailed a second reminder including a HPV self-sampling kit; 2) Mailed a second reminder offering a HPV self-sampling kit, to be ordered by e-mail, text message, phone, or through a webpage; and 3) Mailed a second reminder for a practitioner-collected sample (control group). The primary outcome will be the proportion of women in the intervention groups who participate by returning their HPV self-sampling kit or have a practitioner-collected sample compared with the proportion of women who have a practitioner-collected sample in the control group at 90 and 180 days after mail out of the second reminders. Per-protocol and intention-to-treat analyses will be performed. The secondary outcome will be the proportion of women with a positive HPV self-collected sample who attend follow-up testing at 30, 60, or 90 days after mail out

of the results. DISCUSSION: The CHOiCE trial will provide strong and important evidence allowing us to determine if and how HPV self-sampling can be used to increase participation in cervical cancer screening. This trial therefore has the potential to improve prevention and reduce the number of deaths caused by cervical cancer. TRIAL REGISTRATION: Current Controlled Trials NCT02680262 . Registered 10 February 2016.

Cervical cancer treatment and late effects
Pernille Tine Jensen
References provided by the speaker:

Hoogendam JP, Verheijen RH, Wegner I, Zweemer RP (2014). "Oncological outcome and long-term complications in robot-assisted radical surgery for early stage cervical cancer: an observational cohort study." BJOG **121**(12): 1538-45.

OBJECTIVE: To report the oncological outcome and long-term complications of radical surgery by robot-assisted laparoscopy in early stage cervical cancer. DESIGN: Observational cohort study. SETTING: Tertiary referral centre. POPULATION: About 100 cervical cancer patients treated consecutively with robot-assisted radical surgery between 2008 and 2013. METHODS: Two gynaecological oncologists specialised in minimally invasive surgery performed all surgeries on a three/four-armed robotic system. Procedures consisted of pelvic lymph node dissection combined with a radical hysterectomy, radical vaginal trachelectomy or parametrectomy. MAIN OUTCOME MEASURES: Recurrence, survival and long-term complication rates. RESULTS: 104 robot-assisted laparoscopies were performed in 100 patients (stage IA1-IIB), with a median follow-up of 29.5 months (range 2.5-67.1 months). Thirteen cases were diagnosed with a loco-regional (8%), distant (4%) or combined (1%) recurrence at a median of 14.4 months (range 2.9-34.8 months). All mortality (7%) was cervical cancer-related and due to recurrent disease. Four recurrences receive palliative care and two are in complete remission. The overall 5-year progression-free and disease-specific survival rates are 81.4 and 88.7%, respectively. Frequent complications were lymphoedema (26%), lower urinary tract symptoms (19%), urinary tract infection (17%) and sexual disorders (9%). Five patients had a vaginal cuff dehiscence. No complication-related mortality occurred. CONCLUSION: The recurrence, survival and long-term complication rates of robot-assisted radical surgery for early stage cervical cancer in this cohort are reassuring concerning its continued clinical use.

Jensen, P. T., M. Groenvold, M. C. Klee, I. Thranov, M. A. Petersen and D. Machin (2003). "Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer." Int J Radiat Oncol Biol Phys **56**(4): 937-949.

PURPOSE: To investigate the longitudinal course of self-reported sexual function and vaginal changes in patients disease free after radiotherapy (RT) for locally advanced, recurrent, or persistent cervical cancer. MATERIALS AND METHODS: A total of 118 patients referred for RT were included. The patients were assessed, using a validated self-assessment questionnaire, at the termination of RT and 1, 3, 6, 12, 18, and 24 months later. The results were compared with an age-matched control group from the general population. RESULTS: Persistent sexual dysfunction and adverse vaginal changes were reported throughout the 2 years after RT, with small changes over time: approximately 85% had low or no sexual interest, 35% had moderate to severe lack of lubrication, 55% had mild to severe dyspareunia, and 30% were dissatisfied with their sexual life. A reduced vaginal dimension was reported by 50% of the patients, and 45% were never, or only occasionally, able to complete sexual intercourse. Despite sexual dysfunction and vaginal adverse effects, 63% of those sexually active before having cancer remained sexually active after treatment, although with a considerably decreased frequency. CONCLUSIONS: Patients who are disease free after RT for locally advanced, recurrent, or persistent cervical cancer are at

high risk of experiencing persistent sexual and vaginal problems compromising their sexual activity and satisfaction.

Green JA, Kirwan JM, Tierney JF, et al. (2001). "Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis." Lancet **358**: 781-6.

BACKGROUND: The US National Cancer Institute alert in February, 1999, stated that concomitant chemotherapy and radiotherapy should be considered for all patients with cervical cancer. Our aim was to review the effects of chemoradiotherapy on overall and progression-free survival, local and distant control, and acute and late toxicity in patients with cervical cancer. METHODS: With the methodology of the Cochrane Collaboration, we did a systematic review of all known randomised controlled trials done between 1981 and 2000 (17 published, two unpublished) of chemoradiation for cervical cancer. FINDINGS: The trials included 4580 randomised patients, and 2865-3611 patients (62-78%) were available for analysis. Cisplatin was the most common agent used. The findings suggest that chemoradiation improves overall survival (hazard ratio 0.71, p<0.0001), whether platinum was used (0.70, p<0.0001) or not (0.81, p=0.20). A greater beneficial effect was seen in trials that included a high proportion of stage I and II patients (p=0.009). An improvement in progression-free survival was also seen with chemoradiation (0.61, p<0.0001). Thus, the absolute benefit in progression-free and overall survival was 16% (95% CI 13-19) and 12% (8-16), respectively. A significant benefit of chemoradiation on both local (odds ratio 0.61, p<0.0001) and distant recurrence (0.57, p<0.0001) was also recorded. Grade 3 or 4 haematological (odds ratio 1.49-8.60) and gastrointestinal (2.22) toxicities were significantly greater in the concomitant chemoradiation group than the control group. There was insufficient data to establish whether late toxicity was increased in the concomitant chemoradiation group. INTERPRETATION: Concomitant chemotherapy and radiotherapy improves overall and progression-free survival and reduces local and distant recurrence in selected patients with cervical cancer, which may give a cytotoxic and sensitisation effect.

Ryu SY, Park SI, Nam BH, et al. (2011). " Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors?" Int J Radiat Oncol Biol Phys **79**:794-9

PURPOSE: To determine whether adjuvant chemoradiotherapy (CRT) improves the outcome of cervical cancer patients with intermediate risk factors. METHODS AND MATERIALS: Between January 2000 and June 2006, the medical records of 735 patients who had undergone radical surgery for Stage IB-IIA cervical cancer were reviewed retrospectively. Of the 735 patients, 172 with two or more intermediate risk factors (i.e., lymphovascular space involvement, deep stromal invasion, and tumor size≥2 cm) were grouped as follows according to the adjuvant treatment received: 34 patients, no further treatment; 49 patients, RT; and 89 patients, CRT. The significance of the clinical parameters and recurrence-free survival of each group were analyzed. RESULTS: Of the 172 patients with any of the intermediate risk factors, 137 (79.6%) had two or more intermediate risk factors. Of the 172 patients, 12 developed recurrences (6.4%)->(7.0%), with 6 in the pelvis and 6 in distant sites. All 12 recurrences occurred in those who had two or more intermediate risk factors (sensitivity, 100%); however, only six recurrences were detected in patients who met the Gynecologic Oncology Group criteria for the intermediate-risk group (sensitivity, 50%; Z test, p<.05). A statistically significant difference was found in the 3-year recurrence-free survival rate among the no further treatment, RT, and CRT groups (67.5%, 90.5%, and 97.5%, respectively; p<.05). The incidence of Grade 3-4 hematologic and gastrointestinal toxicities was not significantly different statistically between the RT and CRT groups (6.1% and 13.4%, respectively; p > .05). CONCLUSION:
Postoperative adjuvant CRT can improve the outcome of cervical cancer patients with intermediate risk factors, with low increase in toxicity.

Lindegaard JC, Fokdal LU, Nielsen SK, Juul-Christensen J, Tanderup K. (2013). "MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective." Acta Oncol **52**: 1510-9.

BACKGROUND: The first Nordic protocol for three-dimensional (3D) planned radiotherapy in locally advanced cervical cancer was the prospective NOCECA study (1994-2000). NOCECA consisted of computed tomography (CT)-based 3D conformal external beam radiotherapy (EBRT) with a simultaneous integrated boost (SIB) to the primary tumour combined with brachytherapy (BT) based on x-ray imaging. In NOCECA the planning aim was to achieve 80 Gy at point A from EBRT and BT combined. However, the balance of dose between EBRT and BT was determined by tumour size at diagnosis with more EBRT dose given to point A and less by BT in more advanced stages. In 2005 image-guided adaptive brachytherapy (IGABT) based on magnetic resonance imaging (MRI) and optimisation of the BT dose distribution to the remaining tumour and cervix at time of BT (HR CTV) was introduced in Aarhus. EBRT remained like in NOCECA until 2008 when the SIB to the primary tumour was abandoned and IMRT was introduced as routine technique. In this study, we report outcome of our first five-year experience with IGABT using our NOCECA cohort as reference. MATERIAL AND METHODS: The NOCECA cohort comprising 99 patients was compared with 140 consecutive patients treated by IGABT. Patients with para-aortic nodes were excluded in NOCECA but were present in 9% of the patients treated with IGABT. No patient in NOCECA received chemotherapy whereas concomitant cisplatin was given to 79% of the IGABT patients. RESULTS: With IGABT actuarial local control was 91% at three years. When comparing NOCECA with IGABT overall survival was significantly improved from 63% to 79% ($p = 0.005$). In parallel, both moderate and severe late morbidity were reduced by about 50% ($p = 0.02$). CONCLUSION: Introduction of IGABT reduced morbidity and generated a very high rate of local control, which likely has improved survival by at least as much as concomitant chemotherapy.

References session 4 via PubMed search

A PubMed search was performed with the following selection criteria: 1) Denmark AND HPV AND vaccination program in the last 10 years: 11 items retrieved in Endnote. 2) Denmark AND cervical screening in the last 10 years: 17 items retrieved in Endnote. 3.a) Denmark AND "cervical cancer" AND prevention; 3.b) Denmark AND "cervical cancer" AND control; 3.c) Denmark AND "cervical cancer" AND treatment in the last 10 years: 367 items retrieved in Endnote. Search results of 3.a, 3.b and 3.c were combined and after removal of duplicates 241 references were withheld.

The list contains a manual selection of publications relevant to session 4.

Andersen, L.L., L.M.Moller and H. M. Gimbel (2015). "Low adherence to cervical cancer screening after subtotal hysterectomy." Dan Med J **62**(12): A5165.

INTRODUCTION: A reason for not recommending subtotal hysterectomy is the risk of cervical pathology. We aimed to evaluate cervical cancer screening and to describe cervical pathology after subtotal and total hysterectomy for benign indications. METHODS: Data regarding adherence to screening and pathology results from the national Danish registry (Patobank) were obtained on women from a randomised clinical trial and an observational study of subtotal versus total abdominal hysterectomy from the time of surgery until 2014. RESULTS: We included 501 women (259 subtotal hysterectomies and 242 total hysterectomies). The mean follow-up time was 14.1 years, and the mean age at follow-up was 62.1 years. After subtotal hysterectomy, 9.7% were not invited for screening. Adherence to screening was 61.4%; 8.5% were not screened. After total hysterectomy, 14.5% were not invited, 6.6% adhered to screening and 65.7% were not screened. We found a minimum of one abnormal test in 28 (10.8%) after subtotal hysterectomy and one after total hysterectomy. No cervical cancers were found. CONCLUSIONS: Adherence to cervical cancer screening after subtotal hysterectomy in a Danish population is suboptimal and some patients have unnecessary tests performed after total hysterectomy. Clarification of the use of cervical/vaginal smears after hysterectomy is needed to identify women at risk of cervical dysplasia or cancer. FUNDING: Research Foundation of Region Zealand, University of Southern Denmark, Nykobing Falster Hospital, Rigs-hospitalet and Roskilde Hospital, Denmark. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01880710.

Avnstorp, M. B., R. G. Jensen, E. Garnaes, M. H. Therkildsen, B. Norrild, L. Specht, C. von Buchwald and P. Homoe (2013). "Human papillomavirus and oropharyngeal cancer in Greenland in 1994-2010." Int J Circumpolar Health **72**: 22386.

BACKGROUND: Oropharyngeal squamous cell carcinoma (OPSCC) is associated with the sexually transmitted human papillomavirus (HPV), smoking and alcohol. In Greenland, a high rate of HPV-induced cervical cancer and venereal diseases are found, which exposes the population for high risk of HPV infection. In Greenland, only girls are included in the mandatory HPV vaccination program. OBJECTIVE: To investigate the annual incidence of OPSCC and the proportion of HPV-associated OPSCC (HPV+ OPSCC) in Greenland in 1994-2010. DESIGN: At Rigshospitalet, University of Copenhagen, we identified all Greenlandic patients diagnosed and treated for OPSCC from 1994 to 2010. Sections were cut from the patient's paraffin-embedded tissue blocks and investigated for p16 expression by immunohistochemistry. HPV analyses were performed with 2 sets of general HPV primers and 1 set of HPV16-specific primer. HPV+ OPSCC was defined as both >75% p16+ cells and PCR positive for HPV. RESULTS: Of 26 Greenlandic patients diagnosed with OPSCC, 17 were males and 9 were females. The proportion of HPV+ OPSCC in the total study period was 22%, without significant changes in the population in Greenland. We found an increase in the proportion of HPV+ OPSCC from 14% in 1994-2001 to 25% in 2002-2010 (p=0.51). Among

males from 20 to 27% (p=0.63) and in females from 0 to 20% (p=0.71). The annual OPSCC incidence increased from 2.3/100,000 (CI=1.2-4.2) in 1994-2001 to 3.8/100,000 (CI=2.4-6.2) in 2002-2010: among males from 2.4/100,000 (CI=1.0-5.7) to 5.0/100,000 (CI=2.9-8.9). CONCLUSION: Even though the population is at high risk of HPV infection, the proportion of 22% HPV+ OPSCC in the total study period is low compared to Europe and the United States. This might be explained by our small study size and/or by ethnic, geographical, sexual and cultural differences. Continuing observations of the OPSCC incidence and the proportion of HPV+ OPSCC in Greenland are needed.

Azerkan, F., K. Zendehdel, P. Tillgren, E. Faxelid and P. Sparen (2008). "Risk of cervical cancer among immigrants by age at immigration and follow-up time in Sweden, from 1968 to 2004." Int J Cancer **123**(11): 2664-2670.

Because of great variation in the prevalence of human papilloma virus infection and other risk factors of cervical cancer worldwide, migrant studies may help further the understanding of the aetiology and improve prevention of cervical cancer. Our aim was to study the risk of invasive cervical cancer among immigrant women. We followed 758,002 immigrants from different countries who resided in Sweden between 1968 and 2004. Age-standardised incidence rates (ASRs) of immigrants were compared with that in their countries of origin. Poisson regression models estimated the relative risks of cervical cancer among immigrants, overall and stratified by age at migration and follow-up time, compared to Swedish-born women. Overall 1,991 of 19,542 observed cases of cervical cancer occurred among immigrants. Generally they had lower ASRs than in their countries of origin, with the exception of Nordic immigrants. Compared to Swedish-born women, we observed a higher relative risk of cervical cancer among immigrants overall (RR = 1.13, 95% CI 1.08-1.18), and particularly among women from Denmark (RR = 1.8, 95% CI 1.6-2.1), Norway (RR = 1.7, 95% CI 1.5-1.9) and Central America (RR = 2.5, 95% CI 1.3-4.9), while the relative risks were lower in immigrants from Eastern Africa (RR = 0.2, 95% CI 0.1-0.6), South Central Asia (RR = 0.4, 95% CI 0.2-0.6) and South Western Asia (RR = 0.5, 95% CI 0.4-0.7). Follow-up time and age at migration were important effect modifiers for cervical cancer risks. We suggest targeted prevention toward high-risk immigrants, specifically older women, in the first 10 years after arrival into their new homeland.

Baandrup, L., M. Blomberg, C. Dehlendorff, C. Sand, K. K. Andersen and S. K. Kjaer (2013). "Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program." Sex Transm Dis **40**(2): 130-135.

Baldur-Felskov, B., C. Dehlendorff, J. Junge, C. Munk and S. K. Kjaer (2014). "Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program." Cancer Causes Control **25**(7): 915-922.

Baldur-Felskov, B., C. Dehlendorff, C. Munk and S. K. Kjaer (2014). "Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women." J Natl Cancer Inst **106**(3): djt460.

Baldur-Felskov, B., C. Munk, T. S. Nielsen, C. Dehlendorff, B. Kirschner, J. Junge and S. K. Kjaer (2015). " Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012." Cancer Causes Control **26**(8): 1105-1116.

Barken, S. S., E. Lynge, E. S. Andersen and M. Rebolj (2013). "Long-term adherence to follow-up after treatment of cervical intraepithelial neoplasia: nationwide population-based study." Acta Obstet Gynecol Scand **92**(7): 852-857.

OBJECTIVE: To measure adherence to annual follow-up among women treated for cervical intraepithelial neoplasia. DESIGN: Prospective, population-based, register study. SETTING: Denmark, 1996-2007. POPULATION: All women treated for cervical intraepithelial neoplasia with conization. METHODS: Treated women were routinely recommended to have follow-up with annual smears for at least 5 years. MAIN OUTCOME MEASURES: Using individually linked nationwide register data on conizations and follow-up tests (smears and biopsies), we calculated the cumulative proportion of treated women undergoing the recommended follow-up. We measured this cumulative proportion conservatively in 15-month intervals for 5 years. RESULTS: Adherence to annual follow-up among 45,984 treated women decreased gradually. In total, 90% of these women obtained at least one smear in the first post-treatment year, but only 40% obtained the recommended tests for 5 years. Five-year adherence was substantially better outside the capital area, for example, the odds ratio for women from Jutland compared with women from the capital area was 1.70 (95% confidence interval 1.60-1.82). CONCLUSIONS: Adherence to follow-up after conization was poor in Denmark. Our findings suggest that because of this poor adherence, recommendations for long-term annual follow-up after treatment of cervical intraepithelial neoplasia may not be highly effective. Shorter follow-up schedules using highly sensitive tests appear attractive.

Barken, S. S., M. Rebolj, E. S. Andersen and E. Lynge (2012). "Frequency of cervical intraepithelial neoplasia treatment in a well-screened population." Int J Cancer **130**(10): 2438-2444.

Treatment of cervical intraepithelial neoplasia (CIN) detectable at screening has helped reduce the incidence of cervical cancer, but has also led to overtreatment. The estimates of overtreatment have often focused on a particular grade of CIN or age group. The aim of this paper was to provide a nationwide population-based estimate of the frequency of CIN treatment per prevented cervical cancer case in a well-screened population. We retrieved the data from the Danish National Population, Patient, Health Insurance, Pathology, and Cancer Registers, and calculated annual age-standardized CIN treatment rates. We estimated the frequency of CIN treatment per prevented cervical cancer case by comparing the cumulative life-time risk of CIN treatment from 1996 onward, with the difference in the cumulative life-time risks of cervical cancer in the prescreening and the screening periods. Since 1996, more than 5,000 CIN treatments were undertaken annually in the population of about 2.2 million women aged 15-84 years, and at present 5.2 CIN treatments are undertaken per 1,000 women aged 20-49. About six women have undergone CIN treatment for each prevented cervical cancer. The frequency of CIN treatment increased after 2004 and at present almost eight women are treated per prevented cervical cancer case. Screening, though effective in reducing the incidence of cervical cancer, leads also to a considerable burden of CIN treatment. Future trends in CIN treatment should be closely monitored.

Blomberg, M., C. Dehlendorff, C. Munk and S. K. Kjaer (2013). "Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated girls in Denmark." Clin Infect Dis **57**(7): 929-934.

Bonde, J., M. Rebolj, D. M. Ejegod, S. Preisler, E. Lynge and C. Rygaard (2014). "HPV prevalence and genotype distribution in a population-based split-sample study of well-screened women using CLART HPV2 human papillomavirus genotype microarray system." BMC Infect Dis **14**: 413.

Bonde, U., J. S. Joergensen, O. Mogensen and R. F. Lamont (2014). "The potential role of HPV vaccination in the prevention of infectious complications of pregnancy." Expert Rev Vaccines **13**(11): 1307-1316.

There is now incontrovertible evidence that HPV is the cause of almost all cases of genital warts, cervical dysplasia and cervical cancer. Moreover the current review of the recent literature on HPV in relation to pregnancy found strong indications that HPV plays an important role in adverse outcomes of

pregnancy. HPV may contribute to infertility and may increase the risk of miscarriage. Recent studies indicate a significant rate of vertical transmission of HPV between mother and child but whether the mode of delivery makes a difference to the risk of transmission remains unknown. HPV infection appears to be correlated with both spontaneous preterm birth and preterm prelabor rupture of the membranes.

Brinth, L. S., K. Pors, A. C. Theibel and J. Mehlsen (2015). "Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus." Vaccine **33**(22): 2602-2605.

BACKGROUND: Infections with human papilloma virus (HPV) can result in cervical, oropharyngeal, anal, and penile cancer and vaccination programs have been launched in many countries as a preventive measure. We report the characteristics of a number of patients with a syndrome of orthostatic intolerance, headache, fatigue, cognitive dysfunction, and neuropathic pain starting in close relation to HPV vaccination. METHODS: Patients were referred for orthostatic intolerance following HPV vaccination. Symptoms of autonomic dysfunction were quantified by standardised questionnaire. The diagnosis of postural orthostatic tachycardia syndrome (POTS) rested on finding a sustained heart rate increment of >30 min(-1) (>40 min(-1) in adolescents) or to levels >120 min(-1) during orthostatic challenge. RESULTS: 35 women aged 23.3 +/- 7.1 years participated. Twenty-five had a high level of physical activity before vaccination and irregular periods were reported by all patients not on treatment with oral contraception. Serum bilirubin was below the lower detection limit in 17 patients. Twenty-one of the referred patients fulfilled the criteria for a diagnosis of POTS (60%, 95%CI 43-77%). All patients had orthostatic intolerance, 94% nausea, 82% chronic headache, 82% fatigue, 77% cognitive dysfunction, 72% segmental dystonia, 68% neuropathic pain. CONCLUSIONS: In a population referred for symptoms of orthostatic intolerance and other symptoms consistent with autonomic dysfunction that began in close temporal association with a quadrivalent HPV vaccination, we identified a 60% prevalence of POTS. Further work is urgently needed to elucidate the potential for a causal link between the vaccine and circulatory abnormalities and to establish targeted treatment options for the affected patients.

Dugue, P. A., E. Lynge, B. Bjerregaard and M. Rebolj (2012). "Non-participation in screening: the case of cervical cancer in Denmark." Prev Med 54(3-4): 266-269.

OBJECTIVE: To determine the impact of comprehensiveness of cytology registration on the proportion of cervical cancer patients without a recent screening history. METHODS: For Danish women diagnosed with cervical cancer in 2003-2007, we used cytology data from the nationwide Danish Pathology Data Bank and the National Health Service Register. In five steps, we included data from an increasing number of cervical screening laboratories into the analysis, and calculated the proportions of screened women who had cytology registered in two screening rounds prior to the cancer diagnosis. RESULTS: In total, 1867 cervical cancer patients were included in the analysis. When looking only at the screening history in the laboratory that diagnosed the cancer, it appeared that only 40% of women were screened in the last two rounds. This proportion increased to 55% when nationwide screening data were used. This corresponded to a 25% decrease in the proportion of patients without a recent screening history. CONCLUSION: The level of comprehensiveness of screening data makes a measurable difference when evaluating the screening histories of women with cervical cancer. It is important that actions for the improvement of a screening program are based on comprehensive cytology registrations.

Dugue, P. A., E. Lynge and M. Rebolj (2014). "Mortality of non-participants in cervical screening: Register-based cohort study." Int J Cancer **134**(11): 2674-2682.

Dugue, P. A., M. Rebolj, P. Garred and E. Lynge (2013). "Immunosuppression and risk of cervical cancer." Expert Rev Anticancer Ther **13**(1): 29-42.

A markedly increased risk of cervical cancer is known in women immunosuppressed due to AIDS or therapy following organ transplantation. The aim of this review is to determine the association between other conditions affecting the immune system and the risk of cervical cancer. Patients with end-stage renal disease seem to be at an increased risk of cervical cancer. A higher risk of cervical precancerous lesions was found in patients with some autoimmune diseases; particularly if treated with immunosuppressants. Among behavioral factors weakening the immune system, smoking appeared to strongly increase the risk of cervical cancer, while poor diet only moderately increased the risk. It is difficult to determine whether sexually transmitted infections other than human papillomavirus infection are independent risk factors. Identifying those groups of women likely to fail in clearing persistent human papillomavirus infections would help individualize screening guidelines and target immune-associated factors in the cervical cancer etiology.

Ejersbo, D. (2008). "[Screening profile of women who have died from cervical cancer]." Ugeskr Laeger **170**(9): 727-730.

INTRODUCTION: Every year about 400 women in Denmark are diagnosed with cervical cancer and more than 175 die from the disease. Studies show that the majority of patients did not participate in screening programmes and that a significant number of non-participants died from the disease compared to participants with two or more previous cervical smears. The aim was to investigate the screening profile of women who died from cervical cancer compared to a control group. MATERIALS AND METHODS: A total of 72 patients were included in a case-control study. Five cases were excluded. One geographical and age-matched control person was drawn by the Danish Civil Registration System. All data files about the disease and screening profile of every case and control person were registered in a data base. The statistics were performed by the chi2-test with Yates correction. RESULTS: 63% of the patients were non-participants compared to 49% of the controls. The study showed that elderly women in particular are insufficiently screened as 65% of cases as well as controls at 60 years or older were non-participants. CONCLUSION: The fact that non-participants suffered from advanced cervical cancers compared to the participants at the time of diagnosis means that increase of the response rate must be the focus of attention in the future.

Fornari, D., M. Rebolj, B. Bjerregard, M. Lidang, I. Christensen, E. Hogdall and J. Bonde (2016). "Hybrid Capture 2 and cobas human papillomavirus assays perform similarly on SurePath samples from women with abnormalities." Cytopathology **27**(4): 249-260.

OBJECTIVE: In two laboratories (Departments of Pathology, Copenhagen University Hospitals of Herlev and Hvidovre), we compared cobas and Hybrid Capture 2 (HC2) human papillomavirus (HPV) assays using SurePath(R) samples from women with atypical squamous cells of undetermined significance (ASCUS) at >/=30 years and women after treatment of cervical intraepithelial neoplasia (CIN). METHODS: Samples from 566 women with ASCUS and 411 women after treatment were routinely tested with HC2 and, thereafter, with cobas. Histological outcomes were retrieved from the Danish Pathology Data Base. We calculated the overall agreement between the assays, and compared their sensitivity and specificity for >/=CIN2. RESULTS: In women with ASCUS, HC2 and cobas testing results were similar in the two laboratories. The overall agreement was 91% (95% CI, 88-93). After CIN treatment, the overall agreement was 87% (95% CI, 82-91) at Herlev and 88% (95% CI, 82-92) at Hvidovre. There were no significant differences in the sensitivity for >/=CIN2 between the two tests [Herlev, 98% (95% CI, 89-100) for HC2 versus 94% (95% CI, 82-99) for cobas; Hvidovre, 97% (95% CI, 83-100) for HC2 versus 100% (95% CI, 88-100) for cobas]. The differences were also not significant for specificity. CONCLUSIONS: In women with

the studied well-defined clinical indications for HPV testing, cobas and HC2 performed similarly in terms of the detection of HPV and >/=CIN2.

Frederiksen, M. E., M. V. Baillet, P. A. Dugue, P. T. Jensen, C. Rygaard, J. Hallas and E. Lynge (2015). "Abnormal cervical cytology and health care use: a population-based register study." Gynecol Oncol **139**(1): 63-69.

OBJECTIVE: This study aimed to assess the long-term use of health care services in women with abnormal cytology results compared to women with normal cytology results. METHODS: We did a nationwide population-based study, using women aged 23 to 59years participating in the national organized cervical cancer screening program. We included a study population of 40,153 women with abnormal cytology (exposed) and 752,627 women with normal cytology (non-exposed). We retrieved data from the Danish Civil Registration System, the Danish Pathology Data Bank, the National Health Service, the National Patient and the National Prescription Register. We calculated the frequencies of contacts to general practitioner (GP), to private psychiatrist and/or psychologist, admissions to hospitals and use of prescription drugs. These frequencies were calculated separately in the 5-year period "before" the cytology result and for the 5-year period "after" the result. RESULTS: During the "before" period exposed women had more contacts to GPs, more contacts to psychologists/psychiatrist, and more hospital admissions than non-exposed women. In both exposed and non-exposed women, health care use increased from the "before" to the "after" period. This increase was significantly higher for exposed than non-exposed women regarding contacts to GP, admissions to hospitals, and drug use. CONCLUSION: Women with abnormal cytology results constitute a selected group with a higher health care use than other women even before they have the abnormal cytology. This difference is further enhanced after the abnormal cytology result.

Frederiksen, M. E., E. Lynge and M. Rebolj (2012). "What women want. Women's preferences for the management of low-grade abnormal cervical screening tests: a systematic review." Bjog **119**(1): 7-19.

BACKGROUND: If human papillomavirus (HPV) testing will replace cytology in primary cervical screening, the frequency of low-grade abnormal screening tests will double. Several available alternatives for the follow-up of low-grade abnormal screening tests have similar outcomes. In this situation, women's preferences have been proposed as a guide for management decisions. OBJECTIVES: To determine women's preferences for the follow-up of low-grade cervical screening abnormalities. SEARCH STRATEGY: Using Medical Subject Headings (MeSH) terms, PubMed was searched for articles published up to December 2010. The reference lists of the retrieved studies were consulted. SELECTION CRITERIA: Studies asking women to state a preference between active follow-up and observation for the management of low-grade abnormalities on screening cytology or HPV tests. DATA COLLECTION AND ANALYSIS: Information on study design, participants and outcomes was retrieved using a prespecified form. Studies were sorted by design. MAIN RESULTS: Thirteen studies were included in the review. In all five studies that surveyed women with abnormal tests before any management had started, two-thirds preferred active follow-up, predominantly as immediate colposcopy, to observation, predominantly as repeated Pap smears. In all but two studies testing other situations, women more often expressed a preference for active follow-up than for observation; however, women appeared to be somewhat more willing to accept observation if reassured of the low risk of cervical cancer. CONCLUSIONS: Even for low-grade abnormal cervical tests, women tend to prefer active management strategies. It may be a challenge to meet their expectations of optimal follow-up when HPV testing is used in primary screening.

Frederiksen, M. E., S. Njor, E. Lynge and M. Rebolj (2015). "Psychological effects of diagnosis and treatment of cervical intraepithelial neoplasia: a systematic review." Sex Transm Infect **91**(4): 248-256.

BACKGROUND: Treatment of cervical intraepithelial neoplasia (CIN) is a common minor surgical procedure to prevent uterine cervical cancer. However, news of an abnormality detected at screening for cancer might cause the woman to worry. OBJECTIVES: To investigate the psychological consequences of CIN diagnosis and treatment in a systematic review. DATA SOURCES: We searched PubMed using Medical Subject Headings (MeSH) terms for articles published from January 1990 to February 2013. We also examined the reference lists of retrieved articles. SELECTION CRITERIA: Quantitative studies measuring psychological outcomes in women with a histological diagnosis or treatment of CIN, and in women having an outcome other than CIN at cervical screening. DATA COLLECTION AND ANALYSIS: We abstracted the data using a pre-specified list of study characteristics and measured outcomes. For studies not reporting statistical testing, we estimated the statistical significance of the differences between the compared groups using unpaired t tests. MAIN RESULTS: From 5099 retrieved abstracts, 16 studies were included. Diagnosis and treatment of CIN were associated with worse psychological outcomes than normal cytology test results, but the impact decreased over time. In several but not all studies, CIN appeared to have similar psychological consequences to abnormal smears. No study showed a difference in psychological outcomes between CIN and cervical cancer diagnosis when these were measured some years after diagnosis. CONCLUSIONS: The studies suggested that CIN diagnosis and treatment have a negative psychological impact. However, this conclusion should be viewed in the context of a paucity of rigorously designed studies.

Fuglsang, K., L. K. Petersen and J. Blaakaer (2015). "Addressing challenges in future surveillance after surgery for early-stage cervical cancer." Int J Gynecol Cancer **25**(2): 309-314.

OBJECTIVE: This study examines surveillance after early-stage cervical cancer surgery. Since the 1980s, the value of surveillance has been discussed continuously. The main question explored is whether surveillance serves the purpose of ensuring early diagnosis of recurrence. MATERIALS AND METHODS: A retrospective cohort study included 389 women with cervical cancer who underwent surgery as the primary treatment modality at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark, from 1996 to 2011. We used data from patient files and the Danish National Pathology Data Bank. The cumulative risk was estimated by the Kaplan-Meier method and tested by the log-rank test. RESULTS: Forty-three women (11%) had recurrence. Only 27% of the recurrent cases were diagnosed at a scheduled surveillance appointment, but they were often asymptomatic and seemed to have a better outcome after treatment compared with the recurrent cases diagnosed at self-referral.The 5-year survival was overall 91.3%, recurrence-free survival was 96%, and cancer-specific survival was 54%. The median recurrence-free interval was 23 months (range, 4-144) for the symptomatic patients and 14 months (range, 4-48) for the asymptomatic patients. The median survival after recurrence was 12 months (range, 2-132) for the symptomatic patients and 156 months (range, 40-180) for the asymptomatic patients. CONCLUSIONS: At the moment, neither the value of surveillance nor the significance of self-referral related to survival after recurrence is known. In this study, those who are diagnosed with recurrence before symptom onset seem to fare better in terms of 5-year survival than those who are diagnosed after self-referral because of symptoms.

Gosvig, C. F., L. D. Huusom, K. K. Andersen, A. K. Duun-Henriksen, K. Frederiksen, A. Iftner, E. Svare, T. Iftner and S. K. Kjaer (2015). "Long-term follow-up of the risk for cervical intraepithelial neoplasia grade 2 or worse in HPV-negative women after conization." Int J Cancer **137**(12): 2927-2933.

Little research has been conducted on the long-term value of human papillomavirus (HPV) testing after conization. We investigated whether cytology adds to the value of a negative HPV test for long-term prediction of cervical intraepithelial neoplasia grade 2 or worse (CIN2+). In addition, we compared risk of

CIN2+ following a negative HPV test in women after conization with that in women from the general population. During 2002-2005, 667 women treated for CIN2+ were tested for HPV and cytology 46 months after conization. Only HPV-negative women were included. Women participating in routine screening were age-matched with post-conization HPV-negative women, leaving 13,230 and 477 women, respectively, for analysis. By linkage to the Pathology Data Bank, we identified all cases of CIN2+ by December 2013. The 3-, 5-, 8- and 10-year risks for CIN2+ were 0.7, 0.9, 2.8 and 5.7% after a negative HPV test and 0.5, 0.8, 2.9 and 6.1% in HPV and cytology-negative women. HPV-negative women in the general population had similar 3-year and 5-year risks of 0.4 and 1.0%; thereafter, they had lower risks of 1.9% at 8 years and 2.7% at 10 years. Our results indicate that HPV testing may be used as a test of cure after conization. In the first 5 years after testing, the risk for CIN2+ of women who were HPV-negative at 34 months after conization was similar to that of HPV-negative women in the general population. After 67 years, however, women who have undergone conization may be at higher risk for CIN2+.

Gosvig, C. F., L. D. Huusom, K. K. Andersen, A. Iftner, L. Cederkvist, E. Svare, T. Iftner and S. K. Kjaer (2013). "Persistence and reappearance of high-risk human papillomavirus after conization." Gynecol Oncol **131**(3): 661-666.

OBJECTIVE: Women with early cervical cancer or intraepithelial neoplasia grades 2 and 3 (CIN2+) are treated by conization; however, they still have a higher risk for subsequent CIN2+ than the general female population. Persistence of high-risk (HR) human papillomavirus (HPV) is a key factor in the development of CIN2+. We investigated persistence and reappearance of type-specific HR HPV infection after conization and evaluated possible co-factors. METHODS: During 2002-2006, cervical swabs from 604 women were collected before conization, at 4-6 months and at 8-12 months after conization. HPV was detected by HC2 and genotyped by LiPAv2. Information on co-factors was collected through a questionnaire. Associations were assessed by multivariate logistic regression analysis. RESULTS: HR HPV persistence rate was 9.5%. The alpha5/6 species were more likely to persist than alpha9 species (OR, 2.28; 95% CI, 1.11-4.70). For single infections, a doubling in viral load at enrolment increased the risk for persistence by 36% (95% CI, 1.13-1.63). In addition, margin status was associated with risk of persistence. Smoking, oral contraceptive use and severity of the cervical lesion did not significantly affect persistence. Among the HPV infections that had cleared, 2.2% reappeared. CONCLUSION: Our study indicates that viral load is important in predicting HPV persistence. The alpha5/6 species were most likely to persist. However, most of these HPV types have a lower carcinogenic potential than the alpha7/alpha9 species and may be by-standers. Further studies are needed to assess whether pre-conization viral load can also predict subsequent CIN2+.

Gosvig, C. F., L. D. Huusom, I. Deltour, K. K. Andersen, A. K. Duun-Henriksen, E. M. Madsen, L. K. Petersen, L. Elving, L. Schouenbourg, A. Iftner, E. Svare, T. Iftner and S. K. Kjaer (2015). "Role of human papillomavirus testing and cytology in follow-up after conization." Acta Obstet Gynecol Scand **94**(4): 405-411.

OBJECTIVE: Adequate follow-up of women who have undergone conization for high-grade cervical lesions is crucial in cervical cancer screening programs. We evaluated the performance of testing for high-risk human papillomavirus (HPV) types, cytology alone, and combined testing in predicting cervical intraepithelial neoplasia grade 2 or worse (CIN2+) after conization. DESIGN: Prospective cohort study. SETTING: Denmark. POPULATION: 667 women attending for conization. METHODS: Cervical specimens were collected during 2002-2006 at first visit after conization for cytological examination and Hybrid Capture 2 detection of high-risk HPV. The women were passively followed until 2 years after first follow-up visit by linkage to the nationwide Pathology Data Bank. RESULTS: At first visit after conization (median time, 3.4 months), 20.4% were HPV-positive and 17.2% had atypical squamous intraepithelial lesions or more severe cytology (ASCUS+). The 2-year incidence of CIN2+ after conization was 3.6%. Sensitivity for

detection of CIN2+ after conization was 81.0% [95% confidence interval (CI) 58.1-94.6] for positive cytology (ASCUS+ threshold) and 95.2% (95% CI 76.2-99.9) for HPV testing and for combined testing. Specificity of ASCUS+ cytology (85.2%; 95% CI 82.0-88.0) was higher than that of HPV testing (82.4%; 95% CI 79.0-85.4) and markedly higher than that of combined testing (73.2%; 95% CI 69.3-76.8). The margin status had no significant added value. CONCLUSIONS: Testing for high-risk HPV three to four months after conization is more sensitive than ASCUS+ cytology for identifying women at risk for relapse of CIN2+ within 2 years. Further studies are needed to evaluate whether HPV testing could be a stand-alone test in follow up after conization.

Hammer, A., E. Mejlgaard, P. Gravitt, E. Hogdall, P. Christiansen, T. Steiniche and J. Blaakaer (2015). "HPV genotype distribution in older Danish women undergoing surgery due to cervical cancer." Acta Obstet Gynecol Scand **94**(11): 1262-1268.

Hammer, K., O. Mogensen and E. O. Hall (2009). "Hope as experienced in women newly diagnosed with gynaecological cancer." Eur J Oncol Nurs **13**(4): 274-279.

AIM: This article presents findings from a hermeneutic-phenomenological study with the aim to investigate the meaning of the lived experience of hope in women newly diagnosed with gynaecological cancer. METHOD: Fifteen women were interviewed the day they were receiving the diagnosis at a gynaecological department of a Danish university hospital. The women, aged 24-87 (median 52 yrs), were diagnosed with ovarian, endometrial, cervical and vulvar cancer. RESULTS: Hope was found to be connected to both diagnosis, cure, family life and life itself and closely tied to hopelessness. The newly received cancer diagnosis made the women oscillate between hope and hopelessness, between positive expectations of getting cured and frightening feelings of the disease taking over. Five major interrelated themes of hope were identified: hope of being cured, cared for and getting back to normal, hope as being active and feeling well, hope as an internal power to maintain integration, hope as significant relationships and hope as fighting against hopelessness. Thus, hope was woven together with hopelessness in a mysterious way; it took command through inner strength and courage based on a trust in being cured and of being in relationship with significant others. CONCLUSION: The findings of the close relationship between the shades of hope and hopelessness support the need for nurses to continue to practice hope-inspiring nursing. Nurses need to understand the complexity of hope and its close connection to hopelessness when newly diagnosed with a threatening disease as cancer; and the findings might help nurses assist patients in fighting hopelessness.

Hansen, B. T., S. K. Kjaer, L. Arnheim-Dahlstrom, K. L. Liaw, K. E. Jensen, L. T. Thomsen, C. Munk and M. Nygard (2014). "Human papillomavirus (HPV) vaccination and subsequent sexual behaviour: evidence from a large survey of Nordic women." Vaccine **32**(39): 4945-4953.

Hasle, H., J. M. Friedman, J. H. Olsen and S. A. Rasmussen (2016). "Low risk of solid tumors in persons with Down syndrome." Genet Med **18**(11): 1151-1157.

PURPOSE: The aim of this study was to investigate cancer incidence in a large cohort of persons with Down syndrome. METHODS: Down syndrome was identified from the Danish Cytogenetic Register. Cancer occurrence was identified by linkage to the Danish Cancer Registry. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated based on observed and expected numbers from rates for all Danish residents. The cohort consisted of 3,530 persons with Down syndrome contributing 89,570 person-years at risk. RESULTS: Acute leukemia risk was highest from 1-4 years of age and remained elevated until age 30. The overall risk of solid tumors was decreased (SIR 0.45; 95% CI 0.34-0.59), especially in persons 50 years or older (SIR 0.27; 95% CI 0.16-0.43). We found a significantly lower risk of lung cancer (SIR 0.10; 95% CI 0.00-0.56), breast cancer (SIR 0.16; 95% CI 0.03-0.47), and cervical cancer

(SIR 0.0; 95% CI 0.00-0.77). Testicular cancer was the only solid tumor with an increased SIR (2.9; 95% CI 1.6-4.8). CONCLUSIONS: The risk of all major groups of solid tumors was decreased, except testicular cancer. Altered screening strategies should be considered for persons with Down syndrome. This unusual pattern of cancer occurrence may help understanding carcinogenesis in the general population.

Hauerberg, L., C. Hogdall, A. Loft, C. Ottosen, S. F. Bjoern, B. J. Mosgaard, L. Nedergaard and H. Lajer (2015). "Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy." Gynecol Oncol **138**(2): 304-310.

OBJECTIVE: To present and evaluate an unselected national single center strategy with fertility preserving trachelectomy in cervical cancer. In 2003 nationwide single-center referral of women for trachelectomies was agreed upon between all Danish departments performing cervical cancer surgery with the purpose of increasing volume, to increase surgical safety and facilitate follow-up. METHODS: Prospective data were recorded in the Danish Gynecological Cancer Database of all Vaginal Radical Trachelectomies (VRT) performed in Denmark between 2002 and 2013. Oncologic, fertility and obstetrical outcomes of 120 unselected consecutive VRTs were assessed. To obtain complete follow-up about fertility treatment, pregnancy and obstetric outcome the women filled out an electronic questionnaire. Median follow-up: 55.7 months. RESULTS: 85.8% of the patients had stage IB1 disease, 68.3% squamous cell carcinomas, 30.0% adenocarcinomas and 1.7% adenosquamous carcinomas. Six recurrences (5.1%) and 2 deaths (1.7%) occurred. Four women with adenocarcinomas (10.5%) had recurrences, compared to two women with squamous cell carcinomas (2.5%). Seventy-two women (60.0%) desired to conceive and 55 women obtained a total of 77 pregnancies. Of the 72 women 40 were referred to fertility treatment. First and second trimester miscarriage rates were 21.6% and 2.7%, respectively. A total of 53 children were born of which 41 were delivered after gestational week 34. CONCLUSION: This unselected national single center referral study confirms the oncological safety of Vaginal Radical Trachelectomy. The complete follow-up regarding reproductive data, reveals a surprisingly extensive need of fertility treatment and due to the rate of prematurity, these pregnancies must be regarded as high-risk pregnancies.

Hestbech, M. S., E. Lynge, J. Kragstrup, V. Siersma, M. Vazquez-Prada Baillet and J. Brodersen (2015). "The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark." BMJ Open **5**(8): e007921.

OBJECTIVES: To explore the interplay between primary and secondary prevention of cervical cancer by estimating future screening outcomes in women offered human papillomavirus (HPV) vaccination when they were sexually naive. DESIGN: Estimation of outcome of liquid-based cytology screening for a post-HPV vaccination cohort using pre-vaccination screening data combined with HPV vaccination efficacy data reported in the literature. SETTING: Denmark. DATA: The number of screening diagnoses at first screen in a pre-vaccination birth cohort was multiplied by reported risk reductions expected for women who were vaccinated for HPV before sexual debut. All identified studies were reviewed by two authors, and weighted pooled estimates of vaccine efficacies were used. MAIN OUTCOME MEASURES: Proportions of positive and false-positive cervical cytologies and positive predictive value (PPV) were calculated using cervical intraepithelial neoplasia (CIN) grade 2+ and 3+ as cut-off values. RESULTS: The proportion of positive screening tests was reduced from 8.7% before vaccination to 6.5% after vaccination, and the proportion of false-positive screening tests using CIN2+ as a cut-off was reduced from 5.5% pre-vaccination to 4.3% post-vaccination, and using CIN3+ as a cut-off from 6.2% to 4.7%. PPVs were reduced from 23% to 19% (cut-off CIN2+), and from 14% to 12% (cut-off CIN3+). CONCLUSIONS: In our calculations, the proportion of positive screening results with liquid-based cytology will be reduced as a consequence of HPV vaccination, but the reduction is small, and the expected decline in PPV is very limited. In this situation, the information general practitioners will have to provide to their patients will be largely unchanged.

Hohwu, L. and F. Bro (2012). "[Contact from general practitioners to unvaccinated girls can increase HPV vaccination consent]." Ugeskr Laeger **174**(14): 942-945.

The aim of the study was to evaluate the impact of general practitioners (GPs) follow-up of unvaccinated girls in the Danish Human Papillomavirus catch-up vaccination programme. Telephone interviews were conducted with the GPs to explore their follow-up procedure. The girls were divided into two groups: 1) girls contacted by their GP and 2) girls not contacted by their GP. Ten months later 61% of the girls, who had been contacted, had started vaccination in the follow-up group compared to 53% of girls, who had not been contacted ($p < 0.02$). Follow-up by GPs increased the likelihood of subsequent vaccination in a group of unvaccinated girls.

Holst, S., J. Wohlfahrt, S. K. Kjaer, M. Kamper-Jorgensen, P. Kern, M. Andersson and A. Koch (2016). "Cervical cancer screening in Greenland, 1997-2011: Screening coverage and trends in the incidence of high-grade cervical lesions." Gynecol Oncol **143**(2): 307-312.

OBJECTIVE: In spite of the high incidence of cervical cancer in Greenland, no assessment has been made of the impact of organized cervical screening, introduced in 1998, in relation to occurrence of high-grade cervical lesions. The objectives of the present study were to estimate coverage of the screening program and to examine possible changes in cervical intraepithelial neoplasia (CIN3) incidence in Greenland during 1997-2011 according to calendar period and age. METHODS: Using nationwide registries, we calculated age-standardized incidence rates for all women born and living in Greenland. To investigate whether possible variation in the incidence of CIN3 were related to differences in screening coverage, we further estimated relative risks of CIN3 within two years of screening among women who participated in the screening program using log-linear binomial regression. RESULTS: Coverage of the screening program was low during 1997-2011 with the highest level of 54% observed in 2011. Peaks in CIN3 incidence of around 300 per 100,000 person-years were observed in 1999 and between 2009 and 2011, while the incidence was lower of approximately 100 per 100,000 person-years between 2000 and 2008. During 2009-2011, the highest incidence was found among women aged 25-34 years. Similar patterns of CIN3 risk according to calendar period and age groups were observed among screened women. CONCLUSIONS: The great variations in CIN3 incidence and low screening coverage observed during 1997-2011 suggest that improvements in the Greenlandic screening program are warranted.

Hounsgaard, L., M. Augustussen, H. Moller, S. K. Bradley and S. Moller (2013). "Women's perspectives on illness when being screened for cervical cancer." Int J Circumpolar Health **72**.

BACKGROUND: In Greenland, the incidence of cervical cancer caused by human papillomavirus (HPV) is 25 per 100,000 women; 2.5 times the Danish rate. In Greenland, the disease is most frequent among women aged 30-40. Systematic screening can identify women with cervical cell changes, which if untreated may cause cervical cancer. In 2007, less than 40% of eligible women in Greenland participated in screening. OBJECTIVE: To examine Greenlandic women's perception of disease, their understanding of the connection between HPV and cervical cancer, and the knowledge that they deem necessary to decide whether to participate in cervical cancer screening. STUDY DESIGN: The methods used to perform this research were 2 focus-group interviews with 5 Danish-speaking women and 2 individual interviews with Greenlandic-speaking women. The analysis involved a phenomenological-hermeneutic approach with 3 levels of analysis: naive reading, structural analysis and critical interpretation. RESULTS: These revealed that women were unprepared for screening results showing cervical cell changes, since they had no symptoms. When diagnosed, participants believed that they had early-stage cancer, leading to feelings of vulnerability and an increased need to care for themselves. Later on, an understanding of HPV as the basis for diagnosis and the realization that disease might not be accompanied by symptoms developed. The outcome for participants was a life experience, which they used to encourage others to participate in

screening and to suggest ways that information about screening and HPV might reach a wider Greenlandic population. CONCLUSION: Women living through the process of cervical disease, treatment and follow-up develop knowledge about HPV, cervical cell changes, cervical disease and their connection, which, if used to inform cervical screening programmes, will improve the quality of information about HPV, cervical cancer and screening participation. This includes that verbal and written information given at the point of screening and diagnosis needs to be complemented by visual imagery.

Ibfelt, E. H., S. K. Kjaer, C. Hogdall, M. Steding-Jessen, T. K. Kjaer, M. Osler, C. Johansen, K. Frederiksen and S. O. Dalton (2013). "Socioeconomic position and survival after cervical cancer: influence of cancer stage, comorbidity and smoking among Danish women diagnosed between 2005 and 2010." Br J Cancer 109(9): 2489-2495.

BACKGROUND: In an attempt to decrease social disparities in cancer survival, it is important to consider the mechanisms by which socioeconomic position influences cancer prognosis. We aimed to investigate whether any associations between socioeconomic factors and survival after cervical cancer could be explained by socioeconomic differences in cancer stage, comorbidity, lifestyle factors or treatment. METHODS: We identified 1961 cases of cervical cancer diagnosed between 2005 and 2010 in the Danish Gynaecological Cancer database, with information on prognostic factors, treatment and lifestyle. Age, vital status, comorbidity and socioeconomic data were obtained from nationwide administrative registers. Associations between socioeconomic indicators (education, income and cohabitation status) and mortality by all causes were analysed in Cox regression models with inclusion of possible mediators. Median follow-up time was 3.0 years (0.01-7.0). RESULTS: All cause mortality was higher in women with shorter rather than longer education (hazard ratio (HR), 1.46; 1.20-1.77), among those with lower rather than higher income (HR, 1.32; 1.07-1.63) and among women aged<60 years without a partner rather than those who cohabited (HR, 1.60; 1.29-1.98). Socioeconomic differences in survival were partly explained by cancer stage and less by comorbidity or smoking (stage- and comorbidity-adjusted HRs being 1.07; 0.96-1.19 for education and 1.15; 0.86-1.52 for income). CONCLUSION: Socioeconomic disparities in survival after cervical cancer were partly explained by socioeconomic differences in cancer stage. The results point to the importance of further investigations into reducing diagnosis delay among disadvantaged groups.

Ingemann-Hansen, O., M. Lidang, I. Niemann, J. Dinesen, U. Baandrup, H. Svanholm and L. Petersen (2008). "Screening history of women with cervical cancer: a 6-year study in Aarhus, Denmark." Br J Cancer **98**(7): 1292-1294.

To identify possible weaknesses in cervical screening in Aarhus County, 10 years after the programme was introduced, screening histories were examined. A major problem for the screening programme was that 31% of women were never screened and 61% under-screened, the latter group being significantly dominated by older women and high-stage tumours.

Intaraphet, S., N. Kasatpibal, M. Sogaard, S. Khunamornpong, J. Patumanond, A. Chandacham, I. Chitapanarux and S. Siriaunkgul (2014). "Histological type-specific prognostic factors of cervical small cell neuroendocrine carcinoma, adenocarcinoma, and squamous cell carcinoma." Onco Targets Ther **7**: 1205-1214.

BACKGROUND: The study aimed to determine the prognostic impact of clinical and pathological factors on survival among patients with small cell neuroendocrine carcinoma (SNEC), adenocarcinoma (ADC), and squamous cell carcinoma (SCC). METHODS: Eligible participants were all patients with histologically confirmed cervical cancer treated at Chiang Mai University Hospital between 1995 and 2011. We included all patients with SNEC and randomly enrolled patients with ADC and SCC. We used competing-risk regression analysis to examine the risk of cancer-related death by histological type. RESULTS: We included 130 (6.2%) women with SNEC, 346 (16.4%) with ADC, and 1,632 (77.4%) with SCC.

Age >60 years (hazard ratio [HR] 4.9, 95% confidence interval [CI] 2.0-12.0) and lymph node involvement (HR 3.0, 95% CI 1.2-7.4) were prognostic factors among surgically-treated patients with SNEC. Deeper stromal invasion (HR 3.6, 95% CI 1.6-8.3) was a prognostic factor in patients with SCC. In patients with advanced SNEC, age >60 years had a strong prognostic impact (HR 2.6, 95% CI 1.0-6.5) while the International Federation of Gynecology and Obstetrics stages III and IV were prognostic factors for patients with advanced stage ADC (HR 2.9, 95% CI 2.0-4.4 and HR 4.5, 95% CI 2.6-7.9, respectively) and SCC (HR 1.7, 95% CI 1.4-2.0 and HR 3.7, 95% CI 2.8-4.9, respectively) compared with the International Federation of Gynecology and Obstetrics stage IIB. CONCLUSION: Clinical and pathological prognostic factors in cervical cancer differed according to histological type. Taking the important prognostic factors for each histological type into consideration may be beneficial for tailored treatment and follow-up planning.

Jensen, H., H. Svanholm, H. Stovring and F. Bro (2009). "A primary healthcare-based intervention to improve a Danish cervical cancer screening programme: a cluster randomised controlled trial." J Epidemiol Community Health **63**(7): 510-515.

BACKGROUND: The proportion of non-attenders in cervical cancer screening is high, and should be minimised. A targeted invitation to women not participating for the last 5 years in cervical screening was evaluated to determine whether it would decrease the number of these women. Increasing general practitioners' attention to the screening programme for cervical cancer was also evaluated to determine whether it would increase participation. METHODS: A cluster randomised controlled trial conducted in the county of Aarhus, Denmark. All women registered with a GP were randomised. Regardless of group allocation, all women received a normal invitation. In the intervention arm, GPs were visited to facilitate quality enhancements of the screening programme, combined with a special targeted invitation to women aged 23-59 registered with the GP but not attending screening for the last 5 years. The main outcome was the proportion of non-attenders and the secondary outcome was coverage rate. RESULTS: 117 129 women registered with 190 GPs were included in the study. 1737 non-attenders had a Papanicolaou smear during follow-up. The decline in non-attenders was 0.87% (95% CI 0.57% to 1.16%) after 9 months in favour of the intervention. A difference of 0.94% (95% CI 0.21% to 1.67%) in the change of coverage rate was observed at 6 months, which increased to 1.97% (95% CI 0.03% to 3.91%) at 9 months in favour of the intervention. CONCLUSION: It is possible to decrease the proportion of non-attenders and increase the coverage rate in a screening programme for cervical cancer using a special targeted invitation to non-attenders combined with a visit to GPs. To further improve participation, other barriers must be identified and addressed.

Jensen, K. E., C. Munk, P. Sparen, L. Tryggvadottir, K. L. Liaw, E. Dasbach, M. Nygard and S. K. Kjaer (2011). "Women's sexual behavior. Population-based study among 65,000 women from four Nordic countries before introduction of human papillomavirus vaccination." Acta Obstet Gynecol Scand **90**(5): 459-467.

OBJECTIVE: Sexual behavior is of public health interest because of the association with reproductive health and sexually transmitted infections such as human papillomavirus, which is the causal factor of cervical cancer. The aim of the study was to describe patterns in women's sexual behavior in four Nordic countries. DESIGN: Population-based cross-sectional study. SETTING: Denmark, Iceland, Norway, and Sweden (November 2004-June 2005). POPULATION: A random sample of 18-45-year-old women from the female population in the four participating Nordic countries. The participation rate ranged from 81.3% in Denmark to 54.5% in Iceland. In total, 65 623 women were included. METHODS: Each participant completed a structured questionnaire containing questions about sociodemographic factors, lifestyle factors and sexual behavior. MAIN OUTCOME MEASURES: Age-specific and country-specific descriptive measures of sexual behavior, notably age at first intercourse and lifetime number of partners. In addition, risk factors for having had multiple (>10) sexual partners were examined. RESULTS: Overall, median age at first intercourse was 16, and 30.2% (95% CI: 29.9-30.6) of the participating women reported having had >/=10 partners. There was great variation with birth cohort but limited variation between countries. The main correlates of multiple sexual partners were increasing age at enrollment, a higher alcohol intake and young age at first intercourse. CONCLUSIONS: These measurements of sexual behavior before the introduction of national human papillomavirus vaccination programs will form the basis for a comparison with a similar survey performed after vaccination has been introduced.

Jensen, K. E., S. Schmiedel, B. Norrild, K. Frederiksen, T. Iftner and S. K. Kjaer (2013). "Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up." Br J Cancer **108**(1): 234-239.

BACKGROUND: Several environmental factors have been associated with increased risks for cervical cancer. We examined whether reproductive history, contraceptive use, or sexual behaviour increase the risk for cervical intraepithelial neoplasia grade 3 or worse (CIN3+) among women with persistent human papillomavirus (HPV) infection. METHODS: A population-based cohort of women participated in a personal interview and underwent a gynaecological examination at which cervical specimens were obtained for HPV DNA testing. Follow-up information (~13 years) on cervical lesions was obtained from the Danish Pathology Data Bank. Women who had a high-risk HPV infection comprised the overall study population (n=1353). A subgroup of women with persistent high-risk HPV infection (n=312) was identified. Hazard ratios (HRs) for a diagnosis of CIN3+ and the corresponding 95% confidence intervals (CIs) were calculated. RESULTS: Women with persistent HPV infection who had given birth had a significantly increased risk for CIN3+ (HR=1.78; 95% CI: 1.07-2.94). No association was found with pregnancy, use of intrauterine devices, or sexual behaviour. Based on small numbers, women with persistent HPV infection had a decreased risk for CIN3+ with any use of oral contraceptives (HR=0.54; 95% CI: 0.29-1.00). CONCLUSION: Childbirth increases the risk for subsequent CIN3+ among women with persistent HPV infection.

Kiellberg Larsen, H., K. Kofoed and C. Sand (2013). "[The disease burden of human papillomavirus in men is substantial and can potentially be prevented]." Ugeskr Laeger **175**(6): 349-353.

Kirkegard, J., D. K. Farkas, M. Sogaard, S. A. Schmidt, E. B. Ostenfeld and D. Cronin-Fenton (2014). "Conization as a marker of persistent cervical human papillomavirus (HPV) infection and risk of gastrointestinal cancer: a Danish 34-year nationwide cohort study." Cancer Causes Control **25**(12): 1677-1682.

PURPOSE: Persistent cervical infection with human papillomavirus (HPV) may be a marker of poor immune function and thus associated with an increased cancer risk. HPV infection is implicated in all cases of cervical cancer, but except for anal and esophageal cancers, the association between persistent HPV infection and gastrointestinal cancer has not been investigated. METHODS: We performed a nationwide population-based cohort study of 83,008 women undergoing cervical conization between 1978 and 2011, using cervical conization as a marker of chronic HPV infection. We computed standardized incidence ratios (SIRs) as a measure of the relative risk of each cancer comparing women undergoing conization with that expected in the general population. We also calculated absolute risks. RESULTS: During follow-up, 988 GI cancers occurred versus 880 expected among 83,008 women followed for a median of 14.9 years, corresponding to a SIR of 1.1 (95 % CI 1.1-1.2). Risks were increased for anal (SIR 2.9; 95 % CI 2.3-3.5) and esophageal (SIR 1.5; 95 % CI 1.1-2.0) cancers, with suggested increased risks of cancers of the gallbladder and biliary tract (SIR 1.3; 95 % CI 0.90-1.8), pancreas (SIR 1.2; 95 % CI 0.97-1.4), and liver (SIR 1.1; 95 % CI 0.79-1.6). The SIRs decreased with increasing follow-up time. The risks of gastric, small intestinal, colon, or rectal cancers were not elevated. Overall, the absolute cancer risk was 0.18 % (95 % CI 0.15-0.21) after 5 years. CONCLUSIONS: The relative risks of several gastrointestinal cancers were raised among women who underwent cervical conization for persistent HPV infection, but the absolute risks were low.

Kirschner, B., S. Poll, C. Rygaard, A. Wahlin and J. Junge (2011). "Screening history in women with cervical cancer in a Danish population-based screening program." Gynecol Oncol **120**(1): 68-72.

OBJECTIVE: The aim of this study was to explore the screening histories of all cervical cancers in a Danish screening population. The intention was to decide suboptimal sides of the screening program and to evaluate the significance of routine screening in the development of cervical cancer. METHODS: The study describes the results of a quality control audit, performed on all new cervical cancer cases diagnosed in the years 2008-2009 at two major Danish screening-centers. All relevant cytological and histological cervical samples were reviewed. RESULTS: 202.534 cytological samples were evaluated in the study period, while 112 women were diagnosed with cervical cancer. The histological diagnoses comprised: 62 (55.4%) squamous cell carcinomas, 20 (17.9%) microinvasive squamous cell carcinomas, 25 (22.3%) adenocarcinomas and 5 cancers of different histology. The mean age of study subjects was 46.6 years. 51 (45.5%) women had deficient screening histories, while 45 (40.2%) women had followed the screening recommendations and had normal cervical samples in review. 11 (9.8%) women were diagnosed with false negative cytology, 2 women had false negative histological tests, while pathological review was not feasible for 3 subjects. CONCLUSIONS: More than 45% of the cervical cancer cases in our study were due to deficient cervical screening, stressing the importance of increasing the screening-uptake and coverage. 40% interval cancers emphasize the relevance of further cervical testing of women with relevant symptoms, despite of prior normal cervical samples. Finally, 9.8% false negative cytological samples are consistent with previous reports, but still a part of the screening program that should be improved.

Kjaer, S. K., G. Breugelmans, C. Munk, J. Junge, M. Watson and T. Iftner (2008). "Population-based prevalence, type- and age-specific distribution of HPV in women before introduction of an HPV-vaccination program in Denmark." Int J Cancer **123**(8): 1864-1870.

Knowledge about the prevalence of human papillomavirus (HPV) on a population level is important. We conducted a large population-based study in Denmark to determine the overall and age-specific HPV prevalence, and HPV type distribution in women. Liquid-based cytology samples (SurePath) were collected consecutively. HPV testing was performed with Hybrid Capture 2 (HC2; Digene) (high-risk and low-risk probes), and LiPA (Innogenetics) was used for genotyping. We analyzed samples from 11,617 women; 94.0% had normal cytology, 4.3% atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion and 1.6% had high-grade squamous intraepithelial lesion (HSIL). The HPV prevalence was 26.4% with a peak in women 20-24 years (50.2%) and then decreased without a

second peak in older women. Among the youngest women (15-19 years), 14% had HPV 16/18 and 16% had HPV 6/11. Prevalence of high-risk HPV types increased from 19.2% in women with normal cytology to 100% in women with cervical intraepithelial neoplasia grade 3 (CIN3)/cervical cancer. HPV 16 was the most prevalent type (6.0% of all women), and was also the most prevalent in women with HSIL (35.1%) and CIN3 (53.2%). Other common HPV types in women with CIN3 included HPV 52, 51, 31, 33 and 18. HPV 16/18 alone was present in 23% of CIN3 lesions and 67% of cervical cancers, and HPV 16/18 together with other high-risk HPV types was present in 41% of CIN3 lesions. This suggests that an efficacious HPV 16/18 vaccine will have a substantial preventive potential in the general female population.

Kjaer, S. K., C. Munk, J. Junge and T. Iftner (2014). "Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention?" Cancer Causes Control **25**(2): 179-189.

Lynge, E., C. Rygaard, M. V. Baillet, P. A. Dugue, B. B. Sander, J. Bonde and M. Rebolj (2014). "Cervical cancer screening at crossroads." Apmis 122(8): 667-673.

Cervical screening has been one of the most successful public health prevention programmes. For 50 years, cytology formed the basis for screening, and detected cervical intraepithelial lesions (CIN) were treated surgically to prevent progression to cancer. In a high-risk country as Denmark, screening decreased the incidence of cervical cancer from 34 to 11 per 100,000, age-standardized rate (World Standard Population). Screening is, however, also expensive; Denmark (population: 5.6 million) undertakes close to half a million tests per year, and has 6-8 CIN-treated women for each prevented cancer case. The discovery of human papillomavirus (HPV) as the cause of cervical cancer dramatically changed perspectives for disease control. Screening with HPV testing was launched around 1990, and preventive HPV vaccination was licensed in 2006. Long-term randomized controlled trials (RCT) demonstrated that HPV testing provides better protection against cervical cancer than cytology, but it requires extra repeated testing. HPV vaccination RCTs, furthermore, have proved that HPV vaccination protects against vaccine-type high-grade CIN in women vaccinated prior to sexual activity, but less so in women vaccinated later. The challenge now is therefore to find an algorithm for screening of a heterogeneous population including non-vaccinated women; women vaccinated prior to start of sexual activity; and women vaccinated later.

Madsen, B. S., H. L. Jensen, A. J. van den Brule, J. Wohlfahrt and M. Frisch (2008). "Risk factors for invasive squamous cell carcinoma of the vulva and vagina--population-based case-control study in Denmark." Int J Cancer **122**(12): 2827-2834.

Mortensen, G. L. (2010). "Drivers and barriers to acceptance of human-papillomavirus vaccination among young women: a qualitative and quantitative study." BMC Public Health **10**: 68.

BACKGROUND: Human papillomavirus (HPV) is a necessary cause of cervical dysplasia and cancer, and of genital warts. Few studies have examined attitudes to HPV vaccination since the introduction of HPV vaccines. We aimed to investigate the reasons for young women's acceptance or rejection of the quadrivalent HPV vaccine after its general availability in Denmark. METHOD: A literature review assessed attitudes towards HPV vaccination and the information was used to identify relevant questions for telephone and focus group interviews with women aged 16-26 who had decided to receive or reject HPV vaccination. 435 women across Denmark were interviewed by telephone. Qualitative interviews were undertaken in focus groups with 33 women living in Odense who had completed the telephone survey. Four focus groups were set up according to age (16-20 and 21-26 years of age) and acceptance/rejection of the vaccine. RESULTS: Of 839 women initially contacted by telephone, 794 were included, 411 (49%) said they accepted vaccination but only 201 (24%) had actually received the vaccine and these latter were

interviewed. 242 women said they refused vaccination of which 234 were interviewed. Women who were undecided were excluded from the study. Prevention of cervical cancer was the main driver for acceptance of the vaccine, followed by parental encouragement and financial support, personal experience of someone with cancer and recommendation by health-care professionals. The greatest barrier to vaccination was its cost. A lack of information about the benefits of vaccination for sexually active women was also an important barrier and the older participants in particular considered that they were too old to be vaccinated. Knowledge about HPV and its role in the development of cervical cancer and genital warts was poor. CONCLUSIONS: The difference between intention to be vaccinated and starting vaccination was considerable, and a large proportion of women aged 16-26 did not wish to be vaccinated. If the most important barriers to vaccination were addressed (cost and a lack of information about vaccination benefits), it is likely that the uptake of vaccination in Denmark would increase substantially.

Mortensen, G. L. and H. K. Larsen (2010). "The quality of life of patients with genital warts: a qualitative study." BMC Public Health **10**: 113.

Nedergaard, B. S., M. Ladekarl, J. R. Nyengaard and K. Nielsen (2008). "A comparative study of the cellular immune response in patients with stage IB cervical squamous cell carcinoma. Low numbers of several immune cell subtypes are strongly associated with relapse of disease within 5 years." Gynecol Oncol **108**(1): 106-111.

OBJECTIVE: The purpose of this study was to investigate possible differences in the primary in situ cellular immune response between patients with and without relapse of Stage IB cervical squamous cell carcinoma. METHOD: Paraffin-embedded tissue from 40 patients (20 with and 20 without relapse) was evaluated. Sections were immunostained for CD1a+, CD3+, CD4+, CD8+, CD20+, CD45RA+, CD45RO+, CD57+, CD68+ and GrB+ cells. Immune cell profile densities were estimated using stereology. RESULTS: We found significantly lower densities of CD3+, CD4+, CD8+ and CD57+ cells (both intra- and peritumoral) in tissue from patients who had relapse. Also densities of intratumoral CD1a+ cells and peritumoral CD20+, CD45RA+ and CD45RO+ cells were significantly lower among patients with relapse. CONCLUSION: This study demonstrates striking differences in the cellular immune response between patients with and without relapse within 5 years. The results are of potential value in adjuvant immunotherapy and prediction of prognosis.

Neumann, G., K. L. Rasmussen and L. K. Petersen (2007). "Cervical adenosquamous carcinoma: tumor implantation in an episiotomy scar." Obstet Gynecol **110**(2 Pt 2): 467-469.

BACKGROUND: We report a rare case of a cervical adenosquamous carcinoma, initially diagnosed during delivery, with subsequent implantation in the episiotomy scar 5 weeks postpartum. CASE: A 35-year-old woman with cervical adenosquamous carcinoma diagnosed during delivery was treated with radical abdominal hysterectomy with bilateral pelvic lymphadenectomy. Five weeks later the metastatic tumor at the episiotomy site was excised, and the patient received adjuvant chemotherapy and radiation therapy. Relapse occurred rapidly, and surgical exenteration was initiated but abandoned intraoperatively due to the presence of intra-abdominal carcinomatosis. The patient was declared terminal 6 months postpartum and died 2 months later. CONCLUSION: This case illustrates the importance of inspection of the perineal area during delivery in patients diagnosed with cervical cancer.

Nielsen, A., S. K. Kjaer, C. Munk and T. Iftner (2008). "Type-specific HPV infection and multiple HPV types: prevalence and risk factor profile in nearly 12,000 younger and older Danish women." Sex Transm Dis **35**(3): 276-282.

Noehr, B., A. Jensen, K. Frederiksen, A. Tabor and S. K. Kjaer (2009). "Loop electrosurgical excision of the cervix and risk for spontaneous preterm delivery in twin pregnancies." Obstet Gynecol **114**(3): 511-515.

OBJECTIVE: To investigate the association between three cervical procedures (biopsy with no treatment, ablation, and loop electrosurgical excision procedure [LEEP]) and subsequent spontaneous preterm delivery in twin pregnancies using population-based data from various nationwide registries. METHODS: : The study population consisted of all twin deliveries in Denmark during a 9-year period, 1997-2005. Information on the deliveries, including cervical procedures, was obtained from various national registries. In all, 9,868 deliveries were eligible for analyses, of which 3,228 were delivered spontaneously preterm (32.7%). Preterm delivery was defined as gestational age between 21 weeks and 37 weeks. Logistic regression analyses were used to evaluate the association between cervical procedures and preterm delivery. RESULTS: Twin pregnancies subsequent to LEEP had a significantly increased risk of overall subsequent spontaneous preterm delivery (43.4%) with an adjusted odds ratio of 1.58 (95% confidence interval 1.16-2.14) compared with pregnancies with no prior LEEP (32.5%). The association was consistent in various secondary analyses and especially strong for the very preterm and extremely preterm groups. We found no increase in risk of preterm delivery subsequent to biopsy without treatment or ablation. CONCLUSION: Our study showed an overall significant increase in risk of preterm delivery in twin pregnancies subsequent to LEEP treatment, even after adjustment for several potential risk factors. LEVEL OF EVIDENCE: II.

Noehr, B., A. Jensen, K. Frederiksen, A. Tabor and S. K. Kjaer (2009). "Loop electrosurgical excision of the cervix and subsequent risk for spontaneous preterm delivery: a population-based study of singleton deliveries during a 9-year period." Am J Obstet Gynecol **201**(1): 33.e31-36.

OBJECTIVE: Our aim was to assess the association between loop electrosurgical excision procedure (LEEP) and the subsequent risk for spontaneous preterm delivery, with the use of population-based data from various nationwide registries. STUDY DESIGN: The study population consisted of all singleton deliveries in Denmark during a 9-year period, 1997-2005. Information on the deliveries that included different cervical procedures was obtained from various national registries. In all, 552,678 deliveries were eligible for analyses. RESULTS: Of the deliveries in which the mother had no previous LEEP, 18,519 deliveries (3.5%) were preterm; when this data were applied to 530 preterm deliveries (6.9%) that were subsequent to LEEP, the yield was a significantly increased risk of preterm delivery, with an odds ratio of 2.07 (95% CI, 1.88-2.27; LEEP vs no LEEP). CONCLUSION: Our study showed an overall 2-fold increase in the risk of spontaneous preterm delivery in singleton deliveries subsequent to LEEP treatment, even after adjustment for various potential risk factors.

Olsen, J. and M. R. Jepsen (2010). "Human papillomavirus transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark." Int J Technol Assess Health Care **26**(2): 183-191.

OBJECTIVES: The objective of this study was to simulate human papillomavirus (HPV) infection in a heterosexual population and subsequently analyze the incremental costs and effects of introducing a vaccination program against HPV types 6, 11, 16, and 18 in Denmark compared with screening alone. METHODS: The analysis was performed in two phases. First, an agent-based transmission model was developed that described the HPV transmission without and with HPV vaccination. Second, an analysis of the incremental costs and effects was performed. The results of prevalence estimates of HPV, genital warts, cervical intraepithelial neoplasia (CIN1-3), and cervical cancer in the model simulations before and after introduction of HPV vaccination were extrapolated to the Danish population figures. Incremental costs and effects were then estimated. Future costs and effects were discounted. RESULTS: Cost-effectiveness ratios for annual vaccination of 12-year-old girls, with a vaccination rate of 70 percent without a catch-up program, were estimated at approximately 1,917 euro per quality-adjusted life-year (QALY, 3 percent discount rate) and 10,846 euro/QALY (5 percent discount rate), given a 62-year time

horizon. CONCLUSIONS: A vaccination program would incur extra vaccination costs but would save treatment costs and improve both quality of life and survival.

Olsen, J. and T. R. Jorgensen (2015). "Revisiting the cost-effectiveness of universal HPV-vaccination in Denmark accounting for all potentially vaccine preventable HPV-related diseases in males and females." Cost Eff Resour Alloc **13**: 4.

OBJECTIVE: The purpose of this study was to assess the consequences of a national immunization program with HPV vaccine for both boys and girls in Denmark, including the prophylactic effects on all potentially vaccine preventable HPV-associated diseases in male and female. METHODS: The study focussed on the quadrivalent vaccine which protects against HPV type 6, 11, 16 and 18, and the vaccine's protection against genital warts, cervical intraepithelial neoplasia, cervical cancer, anogenital cancer (anal, penile, vaginal and vulvar cancer) and head and neck cancer (oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancer) were included in the analyses. In general, the analysis was performed in two phases. First, an agent-based transmission model that described the HPV transmission without and with HPV vaccination was applied. Second, an analysis of the incremental costs and effects was performed. The model did not include naturally-acquired immunity to HPV in the simulations. RESULTS: In the base case result (i.e. vaccination of girls only, 85% vaccination rate, private market price at euro 123 per dose ex. VAT) an ICER of 3583 euro/QALY (3-dose regime) is estimated when all HPV-related diseases are taken into account. Vaccination of girls & boys vs. vaccination of girls only an ICER of 28,031 euro/QALY (2-dose regime) and 41,636 euro/QALY (3-dose regime) is estimated. CONCLUSIONS: Extension of the current HPV programme in Denmark to include boys and girls is a cost effective preventive intervention that would lead to a faster prevention of cancers, cancer precursors and genital warts in men and women.

Olsen, J., T. R. Jorgensen, K. Kofoed and H. K. Larsen (2012). "Incidence and cost of anal, penile, vaginal and vulvar cancer in Denmark." BMC Public Health **12**: 1082.

Or Knudsen, A., D. Schledermann, G. B. Nyvang, O. Mogensen and J. Herrstedt (2016). "Trends in gynecologic cancer among elderly women in Denmark, 1980-2012." Acta Oncol **55 Suppl 1**: 65-73.

BACKGROUND: The aim of this analysis was to describe trends in incidence, mortality, prevalence, and survival in Danish women with gynecologic cancer from 1980-2012 comparing women aged 70 years or more with younger women. MATERIAL AND METHODS: Gynecologic cancers included were ICD-10 codes C53 (cancer of the cervix uteri), C54 (corpus uteri cancer), C56 (ovarian cancer) and C57 (Fallopian tube cancer). Data derived from the NORDCAN database with comparable data on cancer incidence, mortality, prevalence and relative survival in the Nordic countries, where the Danish data are delivered from the Danish Cancer Registry and the Danish Cause of Death Registry with follow-up for death or emigration until the end of 2013. RESULTS: For cervical cancer the incidence decreased among women aged less than 70 years and remained stable among the elderly. The mortality rates were clearly separated by age groups with a 2-3 fold higher mortality rate among 70 + years-old than younger women. The mortality rates, however, decreased in all age groups from 1980-2012. For ovarian and Fallopian tube cancers the incidence was almost constant, whereas the average annual number of deaths decreased over time from 466 in 1980 to 396 in 2012. The mortality rates were clearly separated by age groups with mortality rates 3-4 times higher among the elderly. The mortality rate decreased among women less than 70 years during the entire period. The average annual number of newly diagnosed corpus uteri cancer increased from 631 in 1980 to 773 in 2012. The mortality rates were clearly separated by age groups with much higher mortality rates among the 70+ years-old as compared with younger women. Overall the mortality rates decreased from 1980 to 2012. CONCLUSION: In gynecologic cancer both mortality rates and survival are age-dependent with a significantly shorter survival in the group of elderly.

Ortoft, G., T. Henriksen, E. Hansen and L. Petersen (2010). "After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy." Bjog **117**(3): 258-267.

OBJECTIVE: To determine the effects of one or two conisations on preterm delivery and perinatal mortality in subsequent pregnancies. DESIGN: A population-based cohort study. SETTING: Aarhus University Hospital. POPULATION: Preterm delivery and mortality rates were evaluated in 721 deliveries after one conisation, and in 37 deliveries after two conisations, and were compared with 390 deliveries after dysplasia and 74 552 deliveries that were not preceded by conisation or dysplasia. METHODS: Cox regression was used to evaluate preterm delivery rates and perinatal mortality. MAIN OUTCOME MEASURES: Birthweight, gestational age (prior to 28, 32, and 37 weeks of gestation, respectively) and perinatal mortality. RESULTS: The risk of preterm delivery was increased after one conisation [adjusted hazard ratios (95% CI): <37 weeks, 2.8 (2.3-3.5); <28 weeks, 4.9 (2.5-9.7)], and was further increased after two conisations [adjusted hazard ratios (95% CI): <37 weeks, 9.9 (6-17); <28 weeks, 9.8 (1.4-70)], compared with no conisation. One conisation was associated with an increased perinatal mortality [<28 weeks, 9.9 (4.0-25)]. All three methods of conisation [large loop excision of the transformation zone, electroknife and cold knife] increased the risk of preterm delivery. CONCLUSIONS: A single conisation was associated with a 2.8-fold increased risk of perinatal death, most likely because of a 4.9-fold increase in extreme preterm delivery. Only 37 patients had two conisations, and the results showed a ten-fold increase in the risk of preterm delivery.

Preisler, S., M. Rebolj, A. Untermann, D. M. Ejegod, E. Lynge, C. Rygaard and J. Bonde (2013). "Prevalence of human papillomavirus in 5,072 consecutive cervical SurePath samples evaluated with the Roche cobas HPV real-time PCR assay." PLoS One 8(3): e59765.

New commercially available Human Papillomavirus (HPV) assays need to be evaluated in a variety of cervical screening settings. Cobas HPV Test (cobas) is a real-time PCR-based assay allowing for separate detection of HPV genotypes 16 and 18 and a bulk of 12 other high-risk genotypes. The aim of the present study, Horizon, was to assess the prevalence of high-risk HPV infections in an area with a high background risk of cervical cancer, where women aged 23-65 years are targeted for cervical screening. We collected 6,258 consecutive cervical samples from the largest cervical screening laboratory in Denmark serving the whole of Copenhagen. All samples were stored in SurePath media. In total, 5,072 samples were tested with cobas, Hybrid Capture 2 High Risk HPV DNA test (HC2) and liquid-based cytology. Of these, 27% tested positive on cobas. This proportion decreased by age, being 43% in women aged 23-29 years and 10% in women aged 60-65 years. HC2 assay was positive in 20% of samples, and cytology was abnormal (>/= atypical squamous cells of undetermined significance) for 7% samples. When only samples without recent abnormalities were taken into account, 24% tested positive on cobas, 19% on HC2, and 5% had abnormal cytology. The proportion of positive cobas samples was higher than in the ATHENA trial. The age-standardized cobas positivity vs. cytology abnormality was 3.9 in our study and 1.7 in ATHENA. If in Copenhagen the presently used cytology would be replaced by cobas in women above age 30 years, an extra 11% of women would based on historical data be expected to have a positive cobas test without an underlying cervical intraepithelial lesion grade 3 or worse. Countries with a high prevalence of HPV infections should therefore proceed to primary HPV-based cervical screening with caution.

Rebolj, M., J. Bonde, S. Preisler, D. Ejegod, C. Rygaard and E. Lynge (2016). "Human Papillomavirus Assays and Cytology in Primary Cervical Screening of Women Aged 30 Years and Above." PLoS One 11(1): e0147326.

In women aged >/= 30 years, Human Papillomavirus testing will replace cytology for primary cervical screening. We compared Hybrid Capture 2 (HC2), cobas, CLART, and APTIMA HPV assays with cytology on 2869 SurePath samples from women undergoing routine screening at 30-65 years in Copenhagen, Denmark. Women with cytological abnormalities were managed according to routine

recommendations, with 92% completeness. Those with cytology-normal/HPV-positive samples (on any of the four assays) were invited for repeated cytology and HPV testing in 1.5 year, and 58% had additional testing. HPV testing detected more >/= CIN3 than cytology (HC2: 35, cobas, CLART: 37, APTIMA: 34, cytology: 31), although statistically the differences were not significant. Cobas and CLART detected significantly more >/= CIN2 than cytology (cobas, CLART: 49, cytology: 39). The proportion of women with false-positive test results (positive test results without >/= CIN3) varied between 3.3% with cytology and 14.9% with cobas. All HPV assays led to significantly more false-positive tests, whereas compared to HC2 cobas and CLART were associated with a significantly higher and APTIMA with a significantly lower proportion. Detection of CIN1 was particularly increased for the three DNA assays. With APTIMA combined with cytological triage, about 20% more women were referred for colposcopy than with cytology screening. With the three DNA assays, the increase was >/= 50%. The number of women with repeated testing was twice as high with APTIMA and almost five times as high with cobas compared to cytology. To our knowledge, Horizon was the only study set in routine practice that compared more than two HPV assays in the same women while also ascertaining the histological status of women with normal cytology/HPV-positive test results. HPV-based screening of Danish women aged 30-65 detected more high-grade CIN but decreased the screening specificity, and increased the demand for additional testing.

Rebolj, M. and E. Lynge (2010). "Incomplete follow-up of positive HPV tests: overview of randomised controlled trials on primary cervical screening." Br J Cancer 103(3): 310-314.

BACKGROUND: It has been suggested that adjustment for incomplete compliance with follow-up in women with positive human papillomavirus (HPV) tests would be appropriate for estimating the true sensitivity of cervical screening with HPV testing. We assessed the compliance and its impact on > or =CIN3 detection in all eight randomised controlled trials (RCT) with published baseline-round data. METHODS: We extracted data on recommended follow-up procedures, follow-up compliance, and > or =CIN3 detection for both arms of each RCT, and assessed their correlation. RESULTS: Compliance with a direct referral for colposcopy was around 90% in all RCTs, whereas compliance with repeated testing among HPV-positive/cytology-negative women was around 60% in three RCTs and 73% in one RCT. Detection of > or =CIN3 was significantly increased in two out of six RCTs with reported data. The correlation between compliance with follow-up in HPV-positive women and relative > or =CIN3 detection was 0.48 (P=0.33). CONCLUSION: There is at present scant evidence to support the view that the measured sensitivity of HPV screening is a simple reflection of compliance with follow-up. Adjustment of measured cervical intraepithelial neoplasia detection on the basis of compliance data may not always be justifiable, and if adjustment is made, it should be used very judiciously.

Rebolj, M., S. H. Njor and E. Lynge (2012). "Restriction of human papillomavirus DNA testing in primary cervical screening to women above age 30: systematic review." Eur J Cancer Prev 21(1): 73-81.

Cervical screening with human papillomavirus (HPV) testing is less specific for high-grade cervical intraepithelial neoplasia (>/=CIN3) than cytology. The aim of this systematic review was to determine whether a restriction of HPV testing to women aged at least 30 years would eliminate the problem. On the basis of the data from randomized controlled trials, we calculated the relative detection of CIN1 and CIN2, and the relative risks of false-positive tests (positive tests without subsequent >/=CIN3) per age group and trial for HPV testing versus cytology. For women aged at least 30 years in trials with a low cytology abnormality rate, detection of CIN1 increased significantly by 50-90% in the two trials with reported data; detection of CIN2 was doubled in three trials; the risks of false-positive HPV tests were also doubled. In trials with a high cytology abnormality rate, these risks were similar for HPV testing and cytology. Adverse effects of HPV testing were for both types of cytology settings, generally higher for women below than above the age of 30. Adverse effects were less common among women aged at least

30 years than among younger women. However, in older women HPV testing still led to more CIN1/CIN2 diagnoses and false-positive tests than cytology.

Rebolj, M., S. Preisler, D. M. Ejegod, C. Rygaard, E. Lynge and J. Bonde (2014). "Disagreement between human papillomavirus assays: an unexpected challenge for the choice of an assay in primary cervical screening." PLoS One 9(1): e86835.

We aimed to determine the disagreement in primary cervical screening between four human papillomavirus assays: Hybrid Capture 2, cobas, CLART, and APTIMA. Material from 5,064 SurePath samples of women participating in routine cervical screening in Copenhagen, Denmark, was tested with the four assays. Positive agreement between the assays was measured as the conditional probability that the results of all compared assays were positive given that at least one assay returned a positive result. Of all 5,064 samples, 1,679 (33.2%) tested positive on at least one of the assays. Among these, 41% tested positive on all four. Agreement was lower in women aged >/= 30 years (30%, vs. 49% at <30 years), in primary screening samples (29%, vs. 38% in follow-up samples), and in women with concurrent normal cytology (22%, vs. 68% with abnormal cytology). Among primary screening samples from women aged 30-65 years (n = 2,881), 23% tested positive on at least one assay, and 42 to 58% of these showed positive agreement on any compared pair of the assays. While 4% of primary screening samples showed abnormal cytology, 6 to 10% were discordant on any pair of assays. A literature review corroborated our findings of considerable disagreement between human papillomavirus assays. This suggested that the extent of disagreement in primary screening is neither population- nor storage media-specific, leaving assay design differences as the most probable cause. The substantially different selection of women testing positive on the various human papillomavirus assays represents an unexpected challenge for the choice of an assay in primary cervical screening, and for follow up of in particular HPV positive/cytology normal women.

Rebolj, M., J. Rask, M. van Ballegooijen, B. Kirschner, K. Rozemeijer, J. Bonde, C. Rygaard and E. Lynge (2015). "Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark." Br J Cancer **113**(9): 1259-1274.

BACKGROUND: We compared the sensitivity and specificity of liquid-based cytology (LBC) and computer-assisted reading for SurePath/FocalPoint and ThinPrep with those of manually read conventional cytology in routine cervical screening in four Danish laboratories. METHODS: Using data from five nationwide registers, technological phases were identified by slide preparation, reading technique, and triage of borderline cytology. Trends in the detection of cervical intraepithelial neoplasia (CIN) were an indicator of the technology's relative sensitivity, and trends in false-positive tests an indicator of relative specificity. RESULTS: At 23-29 years, SurePath/FocalPoint statistically significantly increased the detection of CIN3 by 85% compared with manually read conventional cytology. The 11% increase with ThinPrep was not significant. At 30-44 years, the increase with SurePath/FocalPoint was 58%; the 16% increase with ThinPrep was not significant. At 45-59 years, both technologies led to nonsignificant decreases in the detection. SurePath/FocalPoint doubled the frequency of false-positive tests at any age. With ThinPrep, these proportions remained the same at 23-29 years, but decreased by two-thirds at 45-59 years. In a fourth laboratory with continuous use of manually read conventional cytology, no such trends were seen. CONCLUSIONS: The sensitivity and specificity of modern LBC and computer-assisted reading technologies may be brand- and age-dependent.

Robinson, K. M., B. Ottesen, K. B. Christensen and A. Krasnik (2009). "Diagnostic delay experienced among gynecological cancer patients: a nationwide survey in Denmark." Acta Obstet Gynecol Scand **88**(6): 685-692.

OBJECTIVE: To examine diagnostic delay among gynecological cancer patients. DESIGN: Nationwide study. SETTING: The cohort comprised all women receiving their first treatment for cervical,

endometrial, or ovarian cancer between 1 October 2006 and 1 December 2007 in four of the five centers for gynecological cancer surgery in Denmark. SAMPLE: Of the 911 women alive, 648 participated, resulting in a response rate of 71.1%; of these, 30.1% were diagnosed with cervical cancer, 31.0% with endometrial cancer, and 38.9% with ovarian cancer. METHODS: Questionnaire survey. MAIN OUTCOME MEASURES: Diagnostic delay calculated as total delay, patient delay, general practitioner referral delay, gynecologist appointment delay, and secondary care delay. RESULTS: Diagnostic delays were found in all parts of the diagnostic pathway. Total diagnostic delay has remained long with a median delay of 12 weeks from the time patients experience symptoms until the time they receive treatment; the 10% experiencing the longest delay wait for >41 weeks. For all types of delay, distributions were non-normal. This indicates that the greatest potential for optimizing clinical outcomes may be among the minority of patients experiencing very long delays. Ovarian cancer patients experienced significantly shorter delays compared with other gynecological cancer patients in all parts of the health care system. CONCLUSIONS: Delays occur in all parts of the diagnostic process, suggesting that a multifaceted approach should be adopted with special focus on reducing the very long delays experienced by some patients. By reducing the total diagnostic delays, outcomes such as three-year survival rates can potentially be improved.

Sand, F. L., C. Munk, S. M. Jensen, M. F. Svahn, K. Frederiksen and S. K. Kjaer (2016). "Long-Term Risk for Noncervical Anogenital Cancer in Women with Previously Diagnosed High-Grade Cervical Intraepithelial Neoplasia: A Danish Nationwide Cohort Study." Cancer Epidemiol Biomarkers Prev **25**(7): 1090-1097.

BACKGROUND: High-risk human papillomavirus (HPV) is essential for developing high-grade cervical intraepithelial neoplasia (CIN2 and CIN3) and has also been associated with noncervical anogenital cancers. However, limited knowledge exists about the long-term risk for anal, vulvar, and vaginal cancer following CIN2 or CIN3 diagnosis. METHODS: In a nationwide cohort study, we followed nearly 2.8 million women born in 1918-1990 who were recorded as living in Denmark between January 1, 1978 and December 31, 2012. The cohort was linked to multiple nationwide registers to obtain information on cancer diagnoses and confounders. Follow-up started when the women reached 18 years, date of immigration, or January 1978, and continued until emigration, death, December 31, 2012, or the date of first diagnosis of anogenital or rectal cancer. RESULTS: Women with a history of CIN2 or CIN3 had higher risks for subsequent anal, vulvar, and vaginal cancer than women with no such history. The relative risks were higher for CIN3 than CIN2. No excess risk was found for rectal cancer. Analyses in which time since first CIN3 was taken into account showed increased relative risks for anal [HR = 4.8; 95% confidence interval (CI), 3.3-7.0], vulvar (HR = 3.2; 95% CI, 2.0-5.3), and vaginal (HR = 5.5; 95% CI, 2.4-12.3) cancers >/=25 years after CIN3 diagnosis. CONCLUSION: Women with a history of CIN2 or CIN3 have a long-term increased relative risk for developing anal, vulvar, and vaginal cancer due to an impaired ability to control a persistent HPV infection. IMPACT: This finding adds to our understanding of the relation between HPV infection and noncervical anogenital cancer.

Sander, B. B., M. Rebolj, P. Valentiner-Branth and E. Lynge (2012). "Introduction of human papillomavirus vaccination in Nordic countries." Vaccine **30**(8): 1425-1433.

INTRODUCTION: Cervical screening has helped decrease the incidence of cervical cancer, but the disease remains a burden for women. Human Papillomavirus (HPV) vaccination is now a promising tool for control of cervical cancer. Nordic countries (Denmark, Finland, Greenland, Iceland, Norway and Sweden) are relatively wealthy with predominantly publicly paid health care systems. The aim of this paper was to provide an update of the current status of introduction of HPV vaccine into the childhood vaccination programs in this region. METHODS: Data on cervical cancer, cervical screening programs, childhood immunization and HPV vaccination programs for Nordic countries were searched via PubMed and various organizations. We furthermore contacted selected experts for information. RESULTS: The incidence of cervical cancer is highest in Greenland (25 per 100,000, age standardized, World Standard

Population, ASW) and lowest in Finland (4 per 100,000 ASW) and rates in the other Nordic countries vary between 7 and 11 per 100,000 ASW. Greenland and Denmark were first to introduce HPV vaccination, followed by Norway. Vaccination programs are underway in Sweden and Iceland, while Finland has just recently recommended introduction of vaccination. HPV vaccination has been intensively debated, in particular in Denmark and Norway. DISCUSSION: In Nordic countries with a moderate risk of cervical cancer and a publicly paid health care system, the introduction of HPV vaccination was a priority issue. Many players became active, from the general public to health professionals, special interest groups, and the vaccine manufacturers. These seemed to prioritize different health care needs and weighed differently the uncertainty about the long-term effects of the vaccine. CONCLUSION: HPV vaccination posed a pressure on public health authorities to consider the evidence for and against it, and on politicians to weigh the wish for cervical cancer protection against other pertinent health issues.

Sander, B. B., M. Vazquez-Prada, M. Rebolj, P. Valentiner-Branth and E. Lynge (2015). "Mothers' and their daughters' use of preventive measures against cervical cancer." Scand J Public Health **43**(4): 415-422.

AIMS: Vaccination against human papillomavirus (HPV) and screening are complementary preventive measures against cervical cancer. In Denmark, screening and vaccination are free of charge for the women. In total, 75% of women are screened and about 90% of girls are vaccinated with at least one dose. Our aim was to determine whether, in Denmark, daughters of unscreened mothers are less likely to be vaccinated against HPV than are daughters of screened mothers. METHODS: We used population-based data from the Danish Patient Register, Health Service Registration, Pathology Data Bank, and Civil Registration System. Individual-level data on screening, vaccination, and vital status until 31 December 2010 were retrieved. Daughters were linked to their mothers through the link provided in the Civil Registration System. The study population included 149,147 girls born in 1993-1997 and their mothers. We calculated birth cohort-specific relative risks (RRs) of non-initiation of HPV vaccination in daughters depending on their mothers' screening status. RESULTS: In total, 8% of girls did not receive any vaccination, and 35% of their mothers were unscreened. Among the 92% of girls receiving at least one vaccine dose, 14% of mothers were unscreened. The birth cohort-specific RRs of non-initiation of vaccination given an unscreened mother varied between 2.16 (95% CI: 2.00-2.33) and 2.83 (95% CI: 2.63-3.05). CONCLUSIONS: The observed association between screening and vaccination suggest that it will be difficult to increase the vaccination coverage by, for example, counselling at the mother's cervical screening appointment. Other measures to increase the coverage with vaccination will be important.

Sando, N., K. Kofoed, C. Zachariae and J. Fouchard (2014). "A reduced national incidence of anogenital warts in young Danish men and women after introduction of a national quadrivalent human papillomavirus vaccination programme for young women--an ecological study." Acta Derm Venereol **94**(3): 288-292.

In January 2009 the human papillomavirus (HPV) vaccine was included in the Danish childhood vaccination programme for girls aged 12 years. A catch-up programme for girls up to 16 years of age was started a couple of months earlier. Based on national register data, anogenital wart (AGW) incidences between January 2001 and December 2011 were estimated. We used chi2 analysis to identify significant trends in proportions of patients diagnosed with AGW in the period before and after inclusion of the HPV vaccine in the program. The development of chlamydia infections was included in this study as a proxy for possible behaviour changes that could affect the AGW incidence. Between 2008 and 2011, a 50% (95% CI 44-56) decrease in AGW incidence was seen among 15-19-year-old men ($p = 0.041$), from 5.2 to 2.6/1,000. Among women, a 67% (95% CI 63-72) decrease from 11.7 to 3.8/1,000 was seen ($p < 0.0001$). The decline in frequency of AGW in young Danish women seems to result from the high coverage of the HPV vaccination programme and young men probably benefit from herd immunity.

Skaaby, T., L. L. Husemoen, T. Jorgensen, J. D. Johansen, T. Menne, P. B. Szecsi, S. Stender, P. Bager, J. P. Thyssen and A. Linneberg (2014). "Associations of filaggrin gene loss-of-function variants and human papillomavirus-related cancer and pre-cancer in Danish adults." PLoS One 9(6): e99437.

PURPOSE: Filaggrin proteins are expressed in the skin, oral cavity, oesophagus, and cervical mucose. Loss-of-function mutations in the filaggrin gene (FLG) reduce filaggrin expression and cause an impaired skin barrier function. We hypothesized that FLG mutation carriers would be more susceptible to human papillomavirus (HPV) infection and thus a higher risk of HPV-related cancer and pre-cancer. We investigated the association of the FLG genotype with incidence of HPV-related cancer of cervix, vagina, vulva, penis, anus and head and neck, and pre-cancer of the cervix. METHODS: We included 13,376 persons from four population-based studies conducted in the same background population in Copenhagen, Denmark. Participants were genotyped for the most common FLG mutations in Europeans. Information on cancer was obtained from The Danish Cancer Registry until 11 July 2011. RESULTS: There were 489 cases of prevalent and 97 cases of incident HPV-related cancer and pre-cancer (median follow-up 11.5 years). There was a statistically significant association between FLG genotype and incident HPV-related cancer and pre-cancer with a hazard ratio, HR = 2.1 (95% confidence intervals, CI: 1.2, 3.7) for FLG mutation carriers vs. wild types. CONCLUSIONS: FLG loss-of-function mutations were associated with higher incidence of HPV-related cancers and pre-cancers that are potentially screening and vaccine preventable.

Slattelid Schreiber, S. M., K. E. Juul, C. Dehlendorff and S. K. Kjaer (2015). "Socioeconomic predictors of human papillomavirus vaccination among girls in the Danish childhood immunization program." J Adolesc Health 56(4): 402-407.

PURPOSE: In 2009, human papillomavirus (HPV) vaccination was introduced in the Danish national childhood immunization program targeting all 12-year-old girls. Previous findings suggest that 10%-13% of girls born in 1996-1997 have not initiated vaccination despite free access. This study aims to identify socioeconomic predictors of initiation and completion of HPV vaccination. METHODS: Girls born in 1996-1997 and their guardians were identified through the Danish Civil Registration System. Information on socioeconomic variables and HPV vaccination status was obtained by linkage to Statistics Denmark and the Danish National Health Insurance Service Register. Through logistic regression, we examined associations between socioeconomic variables and HPV vaccine initiation (N = 65,926) and completion (N = 61,162). RESULTS: Girls with immigrant ethnicity (odds ratio [OR] = .49; 95% confidence interval [CI], .42-.57) had lower HPV vaccine initiation than Danish girls. Girls of mothers with basic education (OR = .75; 95% CI, .69-.82) or low disposable income (OR = .67; 95% CI, .61-.73) had decreased initiation compared with girls of mothers with higher education/income. Girls of unemployed mothers (OR = .75; 95% CI, .69-.82) or mothers being unmarried (OR = .70; 95% CI, .65-.76) had lower initiation than girls of employed or married mothers. Finally, vaccine initiation varied depending on place of residence. The predictors of HPV vaccine completion were similar to those of initiation. CONCLUSIONS: We found social inequality in the initiation and completion of HPV vaccination despite free access. As socioeconomic risk factors identified for cervical cancer also are associated with decreased HPV vaccination, social inequalities in cervical cancer have the potential to increase.

Stensen, S., S. K. Kjaer, S. M. Jensen, K. Frederiksen, J. Junge, T. Iftner and C. Munk (2016). "Factors associated with type-specific persistence of high-risk human papillomavirus infection: A population-based study." Int J Cancer 138(2): 361-368.

Persistent genital infection with high-risk (HR) human papillomavirus (HPV) is a prerequisite for cervical cancer development. The aim of this study was to identify factors associated with type-specific persistence of HR HPV infections. From a population-based cohort of 40,399 women participating in cervical cancer screening established during 2002-2005, we selected all HR HPV-positive women (N =

7,778). During follow-up (2005-2008), we collected cervical samples from these women and tested them for HPV DNA to determine type-specific HR HPV persistence in the interval 1-4.5 years after enrolment. Data on hospitalisations, prescriptions and socioeconomic factors were obtained from nationwide registers. Women with abnormal cytology at baseline or who had undergone conisation during follow-up were excluded. Factors associated with persistence were identified by logistic regression analysis. The overall rate of HR HPV persistence was 31.4%. The risk for persistence was significantly increased among women with a previous episode of genital warts (OR, 1.35; 95% CI, 1.04-1.74), current use of oral contraceptives (OR, 1.35; 95% CI, 1.13-1.63) or use of systemic glucocorticoids (OR, 2.04; 95% CI, 1.16-3.56). The number of pregnancies or births or use of a hormonal intrauterine device, hormonal therapy or nonsteroidal anti-inflammatory drugs was not associated with risk for HR HPV persistence. A history of genital warts and current use of oral contraceptives or systemic glucocorticoids increased the risk, potentially indicating a decreased immune response to HPV infection. These findings suggest that host immune response characteristics are important in HR HPV persistence and consequently in cervical cancer development.

Tranberg, M., M. B. Larsen, E. M. Mikkelsen, H. Svanholm and B. Andersen (2015). "Impact of opportunistic testing in a systematic cervical cancer screening program: a nationwide registry study." BMC Public Health **15**: 681.

BACKGROUND: Systematic screening for precancerous cervical lesions has resulted in decreased incidence and mortality of cervical cancer. However, even in systematic screening programs, many women are still tested opportunistically. This study aimed to determine the spread of opportunistic testing in a systematic cervical cancer screening program, the impact of opportunistic testing in terms of detecting cytological abnormalities and examine the associations between sociodemography and opportunistic testing. METHODS: A nationwide registry study was undertaken including women aged 23-49 years (n = 807,624) with a cervical cytology between 2010 and 2013. The women were categorised into: 1) screening after invitation; 2) routine opportunistic testing, if they were either tested more than 9 months after the latest invitation or between 2.5 years and 3 years after the latest cervical cytology and 3) sporadic opportunistic testing, if they were tested less than 2.5 years after the latest cervical cytology. Cytological diagnoses of women in each of the categories were identified and prevalence proportion differences (PPD) and 95% confidence intervals (CIs) were used to explore group differences. Associations between sociodemography and undergoing opportunistic testing were established by multinomial logistic regression. RESULTS: In total, 28.8% of the cervical cytologies were due to either routine (20.7%) or sporadic (8.1%) opportunistic testing. Among women undergoing routine opportunistic testing, a larger proportion had high-grade squamous intraepithelial abnormalities than invited women (PPD: 0.6%, 95 % CI: 0.03-1.17%). A similar proportion of cytological abnormalities among women undergoing sporadic opportunistic testing and invited women was found. In multivariate analyses, younger age, being single or a social welfare recipient and residence region (North Denmark) were especially associated with opportunistic testing (routine or sporadic). CONCLUSIONS: One fourth of cervical cytologies in this study were collected opportunistically. Compared to invited women, women undergoing routine opportunistic testing were more likely to be diagnosed with abnormal cytologies. Hence, routine opportunistic testing might serve as an important supplement to the systematic screening program by covering non-participating women who may otherwise be tested with a delay or not tested at all. Among women tested more often than recommended (sporadic testing), no benefits in terms of detecting more cytological abnormalities were identified.

Thomsen, L. T., M. Nygard, S. Stensen, B. Terning Hansen, L. Arnheim Dahlstrom, K. L. Liaw, C. Munk and S. K. Kjaer (2016). "Awareness of human papillomavirus after introduction of HPV vaccination: a large population-based survey of Scandinavian women." Eur J Cancer Prev.

Thorsteinsson, K., S. Ladelund, S. Jensen-Fangel, T. L. Katzenstein, I. S. Johansen, G. Pedersen, J. Junge, M. Helleberg, M. Storgaard, N. Obel and A. M. Lebech (2016). "Incidence of cervical dysplasia and cervical cancer in women living with HIV in Denmark: comparison with the general population." HIV Med 17(1): 7-17.

OBJECTIVES: Women living with HIV (WLWH) are reportedly at increased risk of invasive cervical cancer (ICC). A recent publication found that WLWH in Denmark attend the national ICC screening programme less often than women in the general population. We aimed to estimate the incidence of cervical dysplasia and ICC in WLWH in Denmark compared with that in women in the general population. METHODS: We studied a nationwide cohort of WLWH and a cohort of 15 age-matched women per WLWH from the general population for the period 1999-2010. Pathology samples were obtained from The Danish Pathology Data Bank, which contains nationwide records of all pathology specimens. The cumulative incidence and hazard ratios (HRs) for time from inclusion to first cervical intraepithelial neoplasia (CIN)/ICC and time from first normal cervical cytology result to first CIN/ICC were estimated. Sensitivity analyses were performed to include prior screening outcome, screening intensity and treatment of CIN/ICC in the interpretation of results. RESULTS: We followed 1140 WLWH and 17 046 controls with no prior history of ICC or hysterectomy for 9491 and 156 865 person-years, respectively. Compared with controls, the overall incidences of CIN1 or worse (CIN1+), CIN2+ and CIN3+, but not ICC, were higher in WLWH and predicted by young age and a CD4 count < 200 cells/muL. In women with normal baseline cytology, incidences of CIN1+ and CIN2+ were higher in WLWH. However, when we compared subgroups of WLWH and controls where women in both groups were adherent to the national ICC screening programme and had a normal baseline cytology, incidences of CIN and ICC were comparable. CONCLUSIONS: Overall, WLWH developed more cervical disease than controls. Yet, in WLWH and controls adherent to the national ICC screening programme and with normal baseline cytology, incidences of CIN and ICC were comparable.

Thorsteinsson, K., M. Storgaard, T. L. Katzenstein, S. Ladelund, F. F. Ronsholt, I. S. Johansen, G. Pedersen, L. Hashemi, L. N. Nielsen, L. Nilas, N. Obel, J. Bonde and A. M. Lebech (2016). "Prevalence and distribution of cervical high-risk human papillomavirus and cytological abnormalities in women living with HIV in Denmark - the SHADE." BMC Cancer 16(1): 866.

BACKGROUND: Women living with HIV (WLWH) are at increased risk of persistent human papillomavirus (HPV) infection, cervical dysplasia and cervical cancer compared with women from the general population (WGP). We assessed the prevalence and distribution of cervical high-risk (hr) HPV infection and cytological abnormalities in WLWH compared with WGP in Denmark. Predictors of HPV and cytological abnormalities were estimated in WLWH. METHODS: WLWH consecutively enrolled in the Study on HIV, cervical Abnormalities and infections in women in Denmark (SHADE) in 2011 and were examined for cervical HPV and cytological abnormalities. WLWH were matched on age and prior cytological findings with WGP from an earlier study. HIV demographics were retrieved from the nationwide Danish HIV Cohort Study. Logistic regression was used to estimate predictors of hrHPV and cytological abnormalities. RESULTS: Of 334 included WLWH 26.4 % were positive for hrHPV as opposed to 16.6 % WGP (p < 0.0001). WLWH had a higher number of multiple infections (>1 h genotype present) (38.5 % versus 25.7 %, p = 0.030). Hr genotypes in descending order of frequency were HPV58 (7.1 %), 52 (5.4 %), and 16 (4.8 %) in WLWH versus HPV16 (4.1 %), 52 (2.8 %) and 58 (2.4 %) in WGP. Predictors of hrHPV in WLWH were short duration of HAART (adjusted OR per year 0.90 (95 % CI 0.84-0.96)), AIDS prior to inclusion (adjusted OR 3.61 (95 % CI 1.75-7.46)), >/=5 lifetime sexual partners (adjusted OR 2.20 (95 % CI 1.08-4.49)), sexual debut <16 years of age (adjusted OR 2.05 (95 % CI 1.03-4.10)) and CD4 < 350 cells/muL (adjusted OR 2.53 (95 % CI 1.20-5.40)). Cytological abnormalities were prevalent in 10.4 % vs. 5.2 % (p = 0.0003) of WLWH and WGP. In WLWH with hrHPV, short duration of HAART predicted cervical dysplasia (adjusted OR per year 0.83 (95 % CI 0.71-0.97)). CONCLUSIONS: WLWH presented with more cervical hrHPV infections and

cytological abnormalities, and a different distribution of hrHPV genotypes compared with WGP. Cervical hrHPV and cytological abnormalities were predicted by short duration of HAART.

Tranberg, M., B. H. Bech, J. Blaakaer, J. S. Jensen, H. Svanholm and B. Andersen (2016). "Study protocol of the CHOiCE trial: a three-armed, randomized, controlled trial of home-based HPV self-sampling for non-participants in an organized cervical cancer screening program." BMC Cancer 16(1): 835.

BACKGROUND: The effectiveness of cervical cancer screening programs is challenged by suboptimal participation and coverage. Offering cervico-vaginal self-sampling for human papillomavirus testing (HPV self-sampling) to non-participants can increase screening participation. However, the effect varies substantially among studies, especially depending on the approach used to offer HPV self-sampling. The present trial evaluates the effect on participation in an organized screening program of a HPV self-sampling kit mailed directly to the home of the woman or mailed to the woman's home on demand only, compared with the standard second reminder for regular screening. METHODS/DESIGN: The CHOiCE trial is a parallel, randomized, controlled, open-label trial. It will include 9327 women aged 30-64 years who are living in the Central Denmark Region and who have not participated in cervical cancer screening after an invitation and one reminder. The women will be equally randomized into three arms: 1) Directly mailed a second reminder including a HPV self-sampling kit; 2) Mailed a second reminder offering a HPV self-sampling kit, to be ordered by e-mail, text message, phone, or through a webpage; and 3) Mailed a second reminder for a practitioner-collected sample (control group). The primary outcome will be the proportion of women in the intervention groups who participate by returning their HPV self-sampling kit or have a practitioner-collected sample compared with the proportion of women who have a practitioner-collected sample in the control group at 90 and 180 days after mail out of the second reminders. Per-protocol and intention-to-treat analyses will be performed. The secondary outcome will be the proportion of women with a positive HPV self-collected sample who attend follow-up testing at 30, 60, or 90 days after mail out of the results. DISCUSSION: The CHOiCE trial will provide strong and important evidence allowing us to determine if and how HPV self-sampling can be used to increase participation in cervical cancer screening. This trial therefore has the potential to improve prevention and reduce the number of deaths caused by cervical cancer. TRIAL REGISTRATION: Current Controlled Trials NCT02680262 . Registered 10 February 2016.

Vandborg, M. P., R. D. Christensen, J. Kragstrup, K. Edwards, P. Vedsted, D. G. Hansen and O. Mogensen (2011). "Reasons for diagnostic delay in gynecological malignancies." Int J Gynecol Cancer 21(6): 967-974.

Von Euler-Chelpin, M., E. Lynge and M. Rebolj (2011). "Register-based studies of cancer screening effects." Scand J Public Health 39(7 Suppl): 158-164.

INTRODUCTION: There are two organised cancer screening programmes in Denmark, against cervical and breast cancers. The aim with this study was to give an overview of the available register-based research regarding these two programmes, to demonstrate the usefulness of data from the national registers. RESEARCH TOPICS: The register-based studies on cancer screening in Denmark could be grouped into research concerning effectiveness, in terms of mortality and incidence reduction, short-term indicators, e.g. in relation to recommended quality assurance indicators, and side effects, e.g. as false-positive results and overdiagnosis. CONCLUSION: The results indicate that registers have proven to be a valuable tool in evaluating the effects of ongoing screening activities. As they cannot be systematically used to test new screening technologies, register-based studies should not be seen as an alternative to randomised controlled trials, but as a supplement.

Widgren, K., J. Simonsen, P. Valentiner-Branth and K. Molbak (2011). "Uptake of the human papillomavirus-vaccination within the free-of-charge childhood vaccination programme in Denmark." Vaccine 29(52): 9663-9667.

BACKGROUND: Persistent infection with human papillomavirus (HPV) is a prerequisite for cervical cancer, which causes 175 yearly deaths and substantial morbidity in Denmark. In January 2009, HPV-vaccination for 12 year-old girls was introduced into the free-of-charge childhood vaccination programme. Due to concerns about potential poor compliance we determined the uptake and identified determinants for vaccination after the first year of the programme. METHODS: All vaccinations given within the vaccination programme are reported to a central register, which we linked to demographic information found in the Danish civil register. We calculated vaccination uptake and used Cox regression survival analysis to compare the uptake rates between demographic subgroups in the population, e.g. by number of siblings, age of mother (at the daughter's birth) and place of origin. RESULTS: The uptake among the 33,838 eligible girls was 80%, 75% and 62% respectively for the three HPV-doses. All subgroups had uptake above 68% for the first HPV-vaccination. Girls with mothers younger or older than the reference group of 25-34 years had a lower uptake rate (adjHR 0.94, 95% CI 0.91-0.97 and adjHR 0.91, 95% CI 0.88-0.94 respectively). Girls with 5 or more siblings had lower uptake rate than girls without siblings (adjHR 0.79, 95% CI 0.71-0.87). Girls born in other EU/EFTA-countries had lower uptake rate than Danish-born girls with Danish-born parents (adjHR 0.74, 95% CI 0.67-0.82). CONCLUSIONS: The introduction of routine HPV-vaccination in Denmark resulted in a relatively high uptake, indicating little reason for major concern about barriers towards the vaccination in Denmark. Population groups with reduced uptake were identified, but as they were small in number their effect on the overall vaccination coverage was marginal. Nonetheless, these groups should be targeted in future acceptance studies and vaccination awareness campaigns.

Zeraiq, L., D. Nielsen and M. Sodemann (2015). "Attitudes towards human papillomavirus vaccination among Arab ethnic minority in Denmark: A qualitative study." Scand J Public Health 43(4): 408-414.

BACKGROUND: Knowledge regarding the human papillomavirus (HPV) and HPV vaccine uptake among ethnic minorities is poorly explored in Denmark. The objective of this study was to explore attitudes and knowledge towards HPV vaccination among Arab mothers and their daughters. METHODS: Five Arabic-speaking focus groups with mothers of vaccine-eligible girls and three focus groups with daughters were conducted. The participants were recruited through different social clubs. A phenomenological approach was used to investigate attitudes and knowledge of HPV vaccination. Meaning condensation inspired by Amedeo Giorgi was used to analyse the transcribed material. RESULTS: A total of 23 women and 13 daughters were included in this study. The mothers' knowledge regarding HPV was limited to the fact that HPV can cause cervical cancer. Two focus groups mentioned that HPV is a sexually transmitted disease and none of the mothers knew that HPV also causes genital warts. Both mothers and daughters acknowledged that the daughters have deeper insight into health-related issues. A gap of knowledge between generations was identified, as mothers and daughters obtained health information from different sources: mothers used the Arabic TV channels as a source of knowledge and daughters had a range of sources, e.g. school, internet, and Western TV channels. The consequence of these differences in obtaining knowledge is that mothers and daughters lack a common language to discuss health issues. Mothers were influenced by Arabic society, while daughters had created a hybrid of Arabic and Danish. Each generation had its own reasons for accepting the vaccine. The level of HPV knowledge and awareness did not affect their uptake decision in that all the participating mothers had accepted the vaccine for their daughters. CONCLUSIONS: Educational programs should target both mothers and daughters because mothers have an inadequate knowledge about HPV. This is likely to bridge the gap of knowledge between mothers and daughters, which constitutes a barrier between the generations.

Session 5 Achievements and challenges in Denmark and lessons learnt

The case of POTS.
Jesper Mehlsen
References provided by the speaker:

Brinth, L., A. C. Theibel, K. Pors and J. Mehlsen (2015). "Suspected side effects to the quadrivalent human papilloma vaccine." Dan Med J **62**(4): A5064.

INTRODUCTION: The quadrivalent vaccine that protects against human papilloma virus types 6, 11, 16 and 18 (Q-HPV vaccine, Gardasil) was included into the Danish childhood vaccination programme in 2009. During the past years, a collection of symptoms primarily consistent with sympathetic nervous system dysfunction have been described as suspected side effects to the Q-HPV vaccine. METHODS: We present a description of suspected side effects to the Q-HPV vaccine in 53 patients referred to our Syncope Unit for tilt table test and evaluation of autonomic nervous system function. RESULTS: All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character. CONCLUSION: We found consistency in the reported symptoms as well as between our findings and those described by others. Our findings neither confirm nor dismiss a causal link to the Q-HPV vaccine, but they suggest that further research is urgently warranted to clarify the pathophysiology behind the symptoms experienced in these patients and to evaluate the possibility and the nature of any causal link and hopefully establish targeted treatment options. FUNDING: not relevant. TRIAL REGISTRATION: not relevant.

Brinth, L. S., K. Pors, A. C. Theibel and J. Mehlsen (2015). "Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus." Vaccine **33**(22): 2602-2605.

BACKGROUND: Infections with human papilloma virus (HPV) can result in cervical, oropharyngeal, anal, and penile cancer and vaccination programs have been launched in many countries as a preventive measure. We report the characteristics of a number of patients with a syndrome of orthostatic intolerance, headache, fatigue, cognitive dysfunction, and neuropathic pain starting in close relation to HPV vaccination. METHODS: Patients were referred for orthostatic intolerance following HPV vaccination. Symptoms of autonomic dysfunction were quantified by standardised questionnaire. The diagnosis of postural orthostatic tachycardia syndrome (POTS) rested on finding a sustained heart rate increment of >30 min(-1) (>40 min(-1) in adolescents) or to levels >120 min(-1) during orthostatic challenge. RESULTS: 35 women aged 23.3 +/- 7.1 years participated. Twenty-five had a high level of physical activity before vaccination and irregular periods were reported by all patients not on treatment with oral contraception. Serum bilirubin was below the lower detection limit in 17 patients. Twenty-one of the referred patients fulfilled the criteria for a diagnosis of POTS (60%, 95%CI 43-77%). All patients had orthostatic intolerance, 94% nausea, 82% chronic headache, 82% fatigue, 77% cognitive dysfunction, 72% segmental dystonia, 68% neuropathic pain. CONCLUSIONS: In a population referred for symptoms of orthostatic intolerance and other symptoms consistent with autonomic dysfunction that began in close temporal association with a quadrivalent HPV vaccination, we identified a 60% prevalence of POTS. Further work is urgently needed to elucidate the potential for a causal link between the vaccine and circulatory abnormalities and to establish targeted treatment options for the affected patients.

Joura, E. A., A. R. Giuliano, O. E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, E. D. Moreira, Jr., Y. Ngan, L. K. Petersen, E. Lazcano-Ponce, P. Pitisuttithum, J. A. Restrepo, G. Stuart, L. Woelber, Y. C. Yang, J. Cuzick, S. M. Garland, W. Huh, S. K. Kjaer, O. M. Bautista, I. S. Chan, J. Chen, R. Gesser, E. Moeller, M. Ritter, S.

Vuocolo and A. Luxembourg (2015). "A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women." N Engl J Med **372**(8): 711-723.

BACKGROUND: The investigational 9-valent viruslike particle vaccine against human papillomavirus (HPV) includes the HPV types in the quadrivalent HPV (qHPV) vaccine (6, 11, 16, and 18) and five additional oncogenic types (31, 33, 45, 52, and 58). Here we present the results of a study of the efficacy and immunogenicity of the 9vHPV vaccine in women 16 to 26 years of age. METHODS: We performed a randomized, international, double-blind, phase 2b-3 study of the 9vHPV vaccine in 14,215 women. Participants received the 9vHPV vaccine or the qHPV vaccine in a series of three intramuscular injections on day 1 and at months 2 and 6. Serum was collected for analysis of antibody responses. Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue were obtained and used for HPV DNA testing, and liquid-based cytologic testing (Papanicolaou testing) was performed regularly. Tissue obtained by means of biopsy or as part of definitive therapy (including a loop electrosurgical excision procedure and conization) was tested for HPV. RESULTS: The rate of high-grade cervical, vulvar, or vaginal disease irrespective of HPV type (i.e., disease caused by HPV types included in the 9vHPV vaccine and those not included) in the modified intention-to-treat population (which included participants with and those without prevalent infection or disease) was 14.0 per 1000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 in a prespecified per-protocol efficacy population (susceptible population) was 0.1 per 1000 person-years in the 9vHPV group and 1.6 per 1000 person-years in the qHPV group (efficacy of the 9vHPV vaccine, 96.7%; 95% confidence interval, 80.9 to 99.8). Antibody responses to HPV-6, 11, 16, and 18 were noninferior to those generated by the qHPV vaccine. Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group. CONCLUSIONS: The 9vHPV vaccine prevented infection and disease related to HPV-31, 33, 45, 52, and 58 in a susceptible population and generated an antibody response to HPV-6, 11, 16, and 18 that was noninferior to that generated by the qHPV vaccine. The 9vHPV vaccine did not prevent infection and disease related to HPV types beyond the nine types covered by the vaccine. (Funded by Merck; ClinicalTrials.gov number, NCT00543543).

Kosalaraksa, P., J. Mehlsen, T. Vesikari, A. Forsten, K. Helm, P. Van Damme, E. A. Joura, K. Ciprero, R. Maansson, A. Luxembourg and A. Sobanjo-ter Meulen (2015). "An open-label, randomized study of a 9-valent human papillomavirus vaccine given concomitantly with diphtheria, tetanus, pertussis and poliomyelitis vaccines to healthy adolescents 11-15 years of age." Pediatr Infect Dis J **34**(6): 627-634.

BACKGROUND: A 9-valent human papillomavirus (9vHPV) vaccine has recently been reported to be safe and highly efficacious against infection and disease related to HPV6/11/16/18/31/33/45/52/58. We evaluated the immunogenicity and safety of the 9vHPV vaccine administered concomitantly with REPEVAX (diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine). METHODS: This open-label, randomized, multicenter study enrolled 1054 males and females ages 11-15 years. Subjects were randomly assigned to each group in a 1:1 ratio. Subjects received a 0.5 mL dose of 9vHPV vaccine intramuscularly at day 1, months 2 and 6 and a 0.5 mL dose of REPEVAX either on day 1 (concomitant vaccination group; n = 526) or at month 1 (nonconcomitant vaccination group, n = 528). Serologic responses for each vaccine component were tested by 1-sided tests of noninferiority between groups. Systemic and injection-site adverse experiences (AEs) and serious AEs were monitored. RESULTS: Noninferiority of anti-HPV geometric mean titers and seroconversion rates for all 9vHPV antigens were demonstrated for the concomitant group compared with the nonconcomitant group. Seroconversion rates for the 9vHPV vaccine types were >/=99.8% in both groups at month 7. For REPEVAX, noninferiority of immune response was established for diphtheria, tetanus, all polio and pertussis antigens for both groups. There were no vaccine-related serious AEs. CONCLUSION: Overall, concomitant administration of 9vHPV vaccine and REPEVAX was generally well tolerated and did not interfere with the immune response

to either vaccine. This strategy would minimize the number of visits required to deliver each vaccine individually.

Care-seeking in females reporting severe adverse reactions to HPV vaccine: Research and policy *perspectives.*

Kåre Mølbak

References provided by the speaker:

Molbak, K., N. D. Hansen and P. Valentiner-Branth (2016). "Pre-Vaccination Care-Seeking in Females Reporting Severe Adverse Reactions to HPV Vaccine. A Registry Based Case-Control Study." PLoS One **11**(9): e0162520.

BACKGROUND: Since 2013 the number of suspected adverse reactions to the quadrivalent human papillomavirus (HPV) vaccine reported to the Danish Medicines Agency (DMA) has increased. Due to the resulting public concerns about vaccine safety, the coverage of HPV vaccinations in the childhood vaccination programme has declined. The aim of the present study was to determine health care-seeking prior to the first HPV vaccination among females who suspected adverse reactions to HPV vaccine. METHODS: In this registry-based case-control study, we included as cases vaccinated females with reports to the DMA of suspected severe adverse reactions. We selected controls without reports of adverse reactions from the Danish vaccination registry and matched by year of vaccination, age of vaccination, and municipality, and obtained from the Danish National Patient Registry and The National Health Insurance Service Register the history of health care usage two years prior to the first vaccine. We analysed the data by logistic regression while adjusting for the matching variables. RESULTS: The study included 316 cases who received first HPV vaccine between 2006 and 2014. Age range of cases was 11 to 52 years, with a peak at 12 years, corresponding to the recommended age at vaccination, and another peak at 19 to 28 years, corresponding to a catch-up programme targeting young women. Compared with 163,910 controls, cases had increased care-seeking in the two years before receiving the first HPV vaccine. A multivariable model showed higher use of telephone/email consultations (OR 1.9; 95% CI 1.2-3.2), physiotherapy (OR 2.1; 95% CI 1.6-2.8) and psychologist/psychiatrist (OR 1.9; 95% CI 1.3-2.7). Cases were more likely to have a diagnosis in the ICD-10 chapters of diseases of the digestive system (OR 1.6; 95% CI 1.0-2.4), of the musculoskeletal system (OR 1.6; 95% CI 1.1-2.2), symptoms or signs not classified elsewhere (OR 1.8; 95% CI 1.3-2.5) as well as injuries (OR 1.5; 95% CI 1.2-1.9). CONCLUSION: Before receiving the first HPV vaccination, females who suspected adverse reactions has symptoms and a health care-seeking pattern that is different from the matched population. Pre-vaccination morbidity should be taken into account in the evaluation of vaccine safety signals.

Progress achieved – real world impact from a Danish perspective.

Susanne Krûger Kjaer

References provided by the speaker:

Baldur-Felskov, B., C. Dehlendorff, J. Junge, C. Munk and S. K. Kjaer (2014). "Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program." Cancer Causes Control **25**(7): 915-922.

Baldur-Felskov, B., C. Dehlendorff, C. Munk and S. K. Kjaer (2014). "Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women." J Natl Cancer Inst **106**(3): djt460.

Blomberg, M., C. Dehlendorff, C. Munk and S. K. Kjaer (2013). "Strongly decreased risk of genital warts after vaccination against human papillomavirus: nationwide follow-up of vaccinated and unvaccinated

girls in Denmark." Clin Infect Dis **57**(7): 929-934.

Blomberg, M., C. Dehlendorff, C. Sand and S. K. Kjaer (2015). "Dose-Related Differences in Effectiveness of Human Papillomavirus Vaccination Against Genital Warts: A Nationwide Study of 550,000 Young Girls." Clin Infect Dis **61**(5): 676-682.

Bollerup, S., B. Baldur-Felskov, M. Blomberg, L. Baandrup, C. Dehlendorff and S. K. Kjaer (2016). "Significant Reduction in the Incidence of Genital Warts in Young Men 5 Years into the Danish Human Papillomavirus Vaccination Program for Girls and Women." Sex Transm Dis **43**(4): 238-242.

BACKGROUND: Denmark introduced the quadrivalent human papillomavirus vaccine into the vaccination program for 12- to 15-year-old girls in 2008 to 2009. In 2012, the program was supplemented with a catch-up program for women aged up to 27 years. We evaluated the effectiveness of the Danish vaccination program on the nationwide incidence of genital warts (GWs), after the second catch-up by including information on both hospital treatments and on self-administered treatment with podophyllotoxin. Genital wart incidence was investigated in both sexes; however, the main focus was on potential herd protection of men. METHODS: Incident cases of GWs were identified from the Danish National Patient Register and through redemptions of prescription for podophyllotoxin in the Danish National Prescription Registry in 2006 to 2013. Age-specific incidence rates (IRs) were assessed, and estimated annual percentage change (EAPC) was calculated by Poisson regression. RESULTS: Genital wart incidence was either stable or increased in both sexes in 2006 to 2008. After introduction of the vaccination program, GW incidence decreased significantly in women aged 12 to 35 years and men aged 12 to 29 years, with rapid decrease among 16- to 17-year-olds (IRwomen, from 1071 to 58 per 100,000 person-years [EAPC, -55.1%; 95% confidence interval, -58.7 to-51.2]; IRmen, from 365 to 77 per 100,000 person-years [EAPC, -36.6%; 95% confidence interval, -40.5 to -32.5] in 2008-2013). CONCLUSIONS: We found a significantly decreasing incidence of GWs in women up to 35 years of age after the start of the human papillomavirus vaccination program. A similar pattern was observed for men aged 12 to 29 years, indicating substantial herd protection.

Evidence-based general practice: prevention among healthy people.
John Brodersen
References provided by the speaker:

Hestbech M., Gyrd-Hansen D., Kragstrup J., Siersma V., Brodersen J. (2016). "How does HPV vaccination status relate to risk perceptions and intention to participate in cervical screening? a survey study." BMC.Public Health **15**:708.

BACKGROUND: Women in several countries will soon be covered by two preventive programmes targeting cervical cancer: HPV vaccination and cervical screening. The HPV vaccines are expected to prevent approximately 70 % of cervical cancers. It has been speculated, that HPV vaccinated women will not attend screening because they falsely think that the vaccine has eliminated their cervical cancer risk. The aim of this study was to investigate the association between HPV vaccination status and perceptions of cervical cancer risk; perceptions of vaccine effect; and intention to participate in cervical screening. Furthermore, to investigate associations between perceptions of cervical cancer risk and intention to participate in cervical screening. METHODS: A random sample of Danish women from the birth cohorts 1993-1995 was invited to complete a web-based questionnaire concerning risk perceptions and intentions to participate in cervical screening. Main outcomes were: perceived lifetime-risk of cervical cancer; perceived HPV vaccine effect; and intention to participate in cervical screening. RESULTS: HPV vaccinated women more often than unvaccinated women intended to participate in screening: adjusted odds ratio

(OR) for being HPV vaccinated when intending to participate in screening of 3.89 (95 % CI: 2.50-6.06). HPV vaccinated women perceived cervical cancer risk to be higher than unvaccinated women did: adjusted OR of 0.11 (95 % CI: 0.03-0.39) and 0.51 (95 % CI: 0.33-0.78) for being HPV vaccinated while having the lowest perception of risk (in two different pre-specified dichotomisations). HPV vaccinated women perceived the vaccine effect to be larger than unvaccinated women did: adjusted OR of 0.31 (95 % CI: 0.18-0.51) and 0.37 (95 % CI: 0.25-0.53) for being HPV vaccinated while having the lowest perception of vaccine effect (in two different pre-specified dichotomisations). There were no associations between perceived cervical cancer risk and intention to participate in screening. CONCLUSIONS: HPV vaccinated women more often than unvaccinated women intended to participate in screening and they perceived cervical cancer risk to be higher and the vaccine effect to be larger than unvaccinated women did. However, in our analyses, risk perceptions could not explain screening intentions neither among vaccinated nor among unvaccinated women.

Brodersen J., Schwartz L.M., Woloshin S. (2014). "Overdiagnosis: How cancer screening can turn indolent pathology into illness." APMIS **122** (8):683-689.

The shift from illness to disease has had a profound impact on modern medicine - particularly in the realm of cancer screening. In screening, it is not patients with illness who seek help from the healthcare system; it is asymptomatic healthy individuals who are invited into the healthcare system to be examined for pathology. The underlying assumption of screening is that abnormalities and pathology always progress. If this were true, it would always make sense to look for disease even when people feel well. The million (or more accurately multi-billion) dollar question is whether the fundamental assumption that disease invariably leads to illness is valid. This is the question that the present paper will try to explore and answer.

Heleno B., Thomsen M.F., Rodrigues D.S., Jørgensen K.J., Brodersen J. (2013). "How frequently are harms quantified in cancer screening trials? A literature review." British Medical Journal **347**:f5334.

Brodersen J., Jørgensen K.J., Gøtzsche P.C. (2010). "The benefits and harm of screening for cancer with focus on breast cancer.**"** The Polish Archives of Internal Medicine **120** (3):89-94.

The balance between benefits and harms is delicate for cancer screening programs. By attending screening with mammography some women will avoid dying from breast cancer or receive less aggressive treatment. But many more women will be overdiagnosed, receive needless treatment, have a false-positive result, or live more years as a patient with breast cancer. Systematic reviews of the randomized trials have shown that for every 2000 women invited for mammography screening throughout 10 years, only 1 will have her life prolonged. In addition, 10 healthy women will be overdiagnosed with breast cancer and will be treated unnecessarily. Furthermore, more than 200 women will experience substantial psychosocial distress for months because of false-positive findings. Regular breast self-examination does not reduce breast cancer mortality, but doubles the number of biopsies, and it therefore cannot be recommended. The effects of routine clinical breast examination are unknown, but considering the results of the breast self-examination trials, it is likely that it is harmful. The effects of screening for breast cancer with thermography, ultrasound or magnetic resonance imaging are unknown. It is not clear whether screening with mammography does more good than harm. Women invited to screening should be informed according to the best available evidence, data should be reported in absolute numbers, and benefits and harms should be reported using the same denominator so that they can be readily compared.

David L. Sackett.(2002). "The arrogance of preventive medicine." Canadian Medical Association Journal **167** (4):363-364.

Comment

Danish Cancer Society initiatives and the background for the initiatives.
Ulla Axelsen

Danish Health Authority: possible efforts to increase HPV vaccine uptake.
Bolette Søborg

References session 5 via PubMed search
No references were searched via PubMed

Session 6 Global achievements and challenges

HPV Programs at a global level
Ikechukwu Ogbuanu

What can we learn from HepB vaccine and other vaccine safety issues?
Mark Kane

References session 6 via PubMed search
No references were searched via PubMed

Part 2: Bibliography of Speakers

List obtained via speaker forms or (if speaker form was not available) via a PubMed search on Name of the speaker. (Ten) most recent articles are shown.

Berit Andersen, Regionshospitalet Randers (Denmark)

Tranberg, M., B. H. Bech, J. Blaakaer, J. S. Jensen, H. Svanholm and B. Andersen (2016). "Study protocol of the CHOiCE trial: a three-armed, randomized, controlled trial of home-based HPV self-sampling for non-participants in an organized cervical cancer screening program." BMC Cancer **16**(1): 835.

Larsen MB, Svanholm S, Andersen B (2016). "An adverse event in a well-established cervical cancer screening program: An observational study of 19,000 women unsubscribed to the program." J Health Leadership **8**: 61-69 doi:10.2147/JHL.S114462

Introduction: In Denmark, an organized approach to cervical cancer screening has had national coverage since 1998. However, in 2013, it was discovered that 19,000 females had been unsubscribed from the Danish National Cervical Cancer Screening Program and had thus not received invitations or reminders as recommended by the health authorities. The study aims to report the essence of this adverse event and describe the outcomes of reestablishing invitations in terms of participation rates and screening results. Furthermore, patient compensations to affected females diagnosed with cervical cancer and coverage in the mass media was reported. Methods: An observational study based on information from the Danish Pathology Databank, the Department of Public Health Programs, and Infomedia (a Danish database of media coverage) was carried out. Results: A total of 19,106 females were affected. Of those still in the screening age, 37.7% had been tested within 3 years or 5 years despite not receiving any invitation. A total of 21.6% reconfirmed their status as unsubscribed. Of the remaining females, 55.6% were tested within a year, and 94.6% of these test results were normal. Among females aged >64 years, 12.7% accepted the offer of a final screening test. Totally, 90% of these tests were normal. Nineteen females diagnosed with cervical cancer were compensated by the Danish Patient Compensation Association with a total of €693,000, ranging from €8,900 to €239,700. Coverage of cervical cancer screening in the mass media increased from 25 items in the 3 months prior to this adverse event to 590 items in the month when it became public. Conclusion: Even though more than one-third of the affected females were tested despite not receiving regular invitations to participate in the screening program, lacking invitations were ranked alongside other adverse events in the health care system if cancer diagnoses were delayed.

Tranberg, M., M. B. Larsen, E. M. Mikkelsen, H. Svanholm and B. Andersen (2015). "Impact of opportunistic testing in a systematic cervical cancer screening program: a nationwide registry study." BMC Public Health **15**: 681.

Ulla Axelsen, Ringshospitalet and Danish Cancer Society (Denmark)

John Brodersen, Centre of Research & Education in General Practice (Denmark)

Hestbech M., Gyrd-Hansen D., Kragstrup J., Siersma V., Brodersen J. "Effects of numerical information on intention to participate in cervical screening among women offered HPV vaccination: A randomised study." Scand.J.Prim.Health Care. Accepted for publication 21 July 2016.

Hestbech M., Gyrd-Hansen D., Kragstrup J., Siersma V., Brodersen J. "How does HPV vaccination status relate to risk perceptions and intention to participate in cervical screening? a survey study." BMC.Public Health 15:708, 2016.

BACKGROUND: Women in several countries will soon be covered by two preventive programmes targeting cervical cancer: HPV vaccination and cervical screening. The HPV vaccines are expected to prevent approximately 70 % of cervical cancers. It has been speculated, that HPV vaccinated women will not attend screening because they falsely think that the vaccine has eliminated their cervical cancer risk. The aim of this study was to investigate the association between HPV vaccination status and perceptions of cervical cancer risk; perceptions of vaccine effect; and intention to participate in cervical screening. Furthermore, to investigate associations between perceptions of cervical cancer risk and intention to participate in cervical screening. METHODS: A random sample of Danish women from the birth cohorts 1993-1995 was invited to complete a web-based questionnaire concerning risk perceptions and intentions to participate in cervical screening. Main outcomes were: perceived lifetime-risk of cervical cancer; perceived HPV vaccine effect; and intention to participate in cervical screening. RESULTS: HPV vaccinated women more often than unvaccinated women intended to participate in screening: adjusted odds ratio (OR) for being HPV vaccinated when intending to participate in screening of 3.89 (95 % CI: 2.50-6.06). HPV vaccinated women perceived cervical cancer risk to be higher than unvaccinated women did: adjusted OR of 0.11 (95 % CI: 0.03-0.39) and 0.51 (95 % CI: 0.33-0.78) for being HPV vaccinated while having the lowest perception of risk (in two different pre-specified dichotomisations). HPV vaccinated women perceived the vaccine effect to be larger than unvaccinated women did: adjusted OR of 0.31 (95 % CI: 0.18-0.51) and 0.37 (95 % CI: 0.25-0.53) for being HPV vaccinated while having the lowest perception of vaccine effect (in two different pre-specified dichotomisations). There were no associations between perceived cervical cancer risk and intention to participate in screening. CONCLUSIONS: HPV vaccinated women more often than unvaccinated women intended to participate in screening and they perceived cervical cancer risk to be higher and the vaccine effect to be larger than unvaccinated women did. However, in our analyses, risk perceptions could not explain screening intentions neither among vaccinated nor among unvaccinated women.

Kolthoff S.K., Hestbech M., Jørgensen K.J., Brodersen J. "Do invitations for cervical screening provide sufficient information to enable informed choice? A cross-sectional study of invitations for publicly funded cervical screening." Journal of the Royal Society of Medicine 109 (7):274-281, 2016.

OBJECTIVE: To investigate whether invitations for publicly funded cervical screening provide sufficient information to enable an informed choice about participation. DESIGN: Cross-sectional study using a checklist of 23 information items on benefits and harms from cervical screening and the risks related to cervical cancer. MATERIAL: Invitations to publicly funded cervical screening in 10 Scandinavian and English-speaking countries. SETTING: Ten Scandinavian and English speaking countries. PARTICIPANTS: Sixteen screening units representing 10 Scandinavian and English speaking countries. MAIN OUTCOME MEASURES: Number of information items presented in invitations for cervical screening. RESULTS: We contacted 21 coordinating units from 11 countries and 20 (95%) responded. Of these, four units did not issue invitations, but the remaining 16 coordinating units in 10 different countries supplied a sample. The invitations for cervical screening were generally information poor and contained a median

of only four out of 23 information items possible (17%), ranging from 0 to 12 (0-52%). The most important harms of cancer screening, overdiagnosis and overtreatment, were typically downplayed or unmentioned. The same applied to other important harms, such as false-positive results and the psychological consequences from an abnormal test result. The majority of invitations took a paternalistic approach. While only two invitations (17%) included a pre-assigned appointment date, eight (70%) of the invitations contained strong appeals for participation. CONCLUSIONS: Invitations to cervical cancer screening were information poor and biased in favour of participation. This means that informed choice is not possible, which is in conflict with modern requirements for personal involvement in medical decisions.

McCaffery K., Jansen J., Scherer L., Thornton H., Hersch J., Carter S., Barratt A., Sheridan S., Moynihan R., Waller J., Brodersen J., Pickles K., Edwards A. "Walking the tightrope: communicating overdiagnosis in modern healthcare." BMJ 352:i348 doi: 10.1136/bmj.i348 (Published 5 February 2016).

Wille M.M., Dirksen A., Ashraf H., Saghir Z., Bach K.S., Brodersen J., Clementsen P.F., Hansen H., Larsen K.R., Mortensen J., Rasmussen J.F., Seersholm N., Skov B.G., Thomsen L.H., Tonnesen P., Pedersen J.H.. "Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-risk Profiling." Am.J Respir.Crit Care Med., 2015.

RATIONALE: As of April 2015, participants in the Danish Lung Cancer Screening Trial had been followed for at least 5 years since their last screening. OBJECTIVES: Mortality, causes of death, and lung cancer findings are reported to explore the effect of computed tomography (CT) screening. METHODS: A total of 4,104 participants aged 50-70 years at the time of inclusion and with a minimum 20 pack-years of smoking were randomized to have five annual low-dose CT scans (study group) or no screening (control group). MEASUREMENTS AND MAIN RESULTS: Follow-up information regarding date and cause of death, lung cancer diagnosis, cancer stage, and histology was obtained from national registries. No differences between the two groups in lung cancer mortality (hazard ratio, 1.03; 95% confidence interval, 0.66-1.6; P = 0.888) or all-cause mortality (hazard ratio, 1.02; 95% confidence interval, 0.82-1.27; P = 0.867) were observed. More cancers were found in the screening group than in the no-screening group (100 vs. 53, respectively; P < 0.001), particularly adenocarcinomas (58 vs. 18, respectively; P < 0.001). More early-stage cancers (stages I and II, 54 vs. 10, respectively; P < 0.001) and stage IIIa cancers (15 vs. 3, respectively; P = 0.009) were found in the screening group than in the control group. Stage IV cancers were nonsignificantly more frequent in the control group than in the screening group (32 vs. 23, respectively; P = 0.278). For the highest-stage cancers (T4N3M1, 21 vs. 8, respectively; P = 0.025), this difference was statistically significant, indicating an absolute stage shift. Older participants, those with chronic obstructive pulmonary disease, and those with more than 35 pack-years of smoking had a significantly increased risk of death due to lung cancer, with nonsignificantly fewer deaths in the screening group. CONCLUSIONS: No statistically significant effects of CT screening on lung cancer mortality were found, but the results of post hoc high-risk subgroup analyses showed nonsignificant trends that seem to be in good agreement with the results of the National Lung Screening Trial. Clinical trial registered with www.clinicaltrials.gov (NCT00496977).

Henriksen M.J.V., Guassora A.D., Brodersen J. "Preconceptions influence women's perceptions of information on breast cancer screening: a qualitative study." BMC.Res.Notes 8, 2015.

BACKGROUND: Screening for breast cancer has been subject to intense debate in recent decades regarding benefits and risks. Participation in breast cancer screening should be based on informed choice, and most countries approach this by sending information leaflets with invitations to attend screening. However, very little attention has been paid to the decision-making process and how the information

leaflets are used and understood by women. The aim of this study is twofold. First, we use a theoretical framework to explore how the framing of information influences the intention to participate in breast cancer screening. Second, we discuss how information and attitudes held prior to receiving the invitation influence the perception of the balance between the benefits and risks harms of screening. METHODS: We used a qualitative design and interviewed six women who were soon to receive their first invitation to participate in the breast screening programme in Denmark. The selected women received a copy of the official information leaflet 1 week before we interviewed them. The six women were interviewed individually using an interview guide based on the theory of planned behaviour. We used meaning condensation for our initial analysis, and further analysis was guided by the theory of cognitive dissonance. RESULTS: For our participants, the decision-making process was dominated by the attitudes of the women's circle of acquaintances and, to a lesser extent, by the information that accompanied the screening invitation. Information that conflicted with attitudes the women already held was actively disregarded. The risk of overdiagnosis as a potentially harmful effect of participation in mammography screening was unknown to the women in our study. An isolated framing effect was not found. CONCLUSION: Women have expectations about breast cancer screening that are formed before they receive information from the screening programme. These expectations compromise the perception of balance between screening benefits and potential harmful effects. They also influence the perception of the information in the breast screening leaflet. The phenomenon of overdiagnosis is unknown to the women.

Hestbech M., Lynge E., Kragstrup J., Siersma V., Baillet M.V-P., Brodersen J. The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark. BMJ Open 5 (8):e007921, 2015.

Johansson M., Hansson A., Brodersen J. "Estimating overdiagnosis in Screening for Abdominal Aortic Aneurysm: could a change in smoking habits and lowered aortic diameter tip the balance of AAA screening towards harm?" BMJ 350:h825, 2015.

Comment

Rasmussen J.F., Siersma V., Pedersen J.H., Brodersen J**.** "Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST)." Lung Cancer 87 (1):65-72, 2015.

OBJECTIVES: To measure the psychosocial consequences in the Danish lung cancer screening trial (DLCST) and compare those between the computed tomography (CT) group and the control group. MATERIALS AND METHODS: This study was a single centre randomised controlled trial with five annual screening rounds. Healthy current or former heavy smokers aged 50-70 years (men and women) were randomised 1:1 to a CT group and a control group. Heavy smokers were defined by having smoked ≥20 pack years and former smokers by being abstinent ≤10 years. Both groups were invited annually to the screening clinic to complete the validated lung-cancer-specific questionnaire consequences of screening lung cancer (COS-LC). The CT group was also offered a low dose CT scan of the lungs. The COS-LC measures nine scales with psychosocial properties: Anxiety, Behaviour, Dejection, Negative impact on sleep, Self-blame, Focus on Airway Symptoms, Stigmatisation, Introvert, and Harm of Smoking. RESULTS: 4104 participants were randomised to the DLCST and the COS-LC completion rates for the CT group and the control group were 95.5% and 73.6%, respectively. There was a significant increase in negative psychosocial consequences from baseline through rounds 2-5 for both the CT group and the control group (mean increase >0, p<.0001 for 3 of 4 possible scales). During rounds 2-5 the control group experienced significantly more negative psychosocial consequences in seven of nine scales compared with the CT group (mean Δ score >0 and p<.033). CONCLUSIONS: Lung cancer CT-screening trials induced more

negative psychosocial reactions in both the CT group and the control group compared with the baseline psychosocial profile. The CT group experienced less negative psychosocial consequences compared with the control group, which might be explained by reassurance among those with normal screening results.

Brodersen J., Schwartz L.M., Woloshin S. "Overdiagnosis: How cancer screening can turn indolent pathology into illness." APMIS 122 (8):683-689, 2014.

The shift from illness to disease has had a profound impact on modern medicine - particularly in the realm of cancer screening. In screening, it is not patients with illness who seek help from the healthcare system; it is asymptomatic healthy individuals who are invited into the healthcare system to be examined for pathology. The underlying assumption of screening is that abnormalities and pathology always progress. If this were true, it would always make sense to look for disease even when people feel well. The million (or more accurately multi-billion) dollar question is whether the fundamental assumption that disease invariably leads to illness is valid. This is the question that the present paper will try to explore and answer.

Pernille Tine Jensen, Odense University Hospital (Denmark)

Frederiksen, M. E., M. V. Baillet, P. A. Dugue, P. T. Jensen, C. Rygaard, J. Hallas and E. Lynge (2015). "Abnormal cervical cytology and health care use: a population-based register study." Gynecol Oncol **139**(1): 63-69.

Froding, L. P., C. Ottosen, B. J. Mosgaard and P. T. Jensen (2015). "Quality of life, urogynecological morbidity, and lymphedema after radical vaginal trachelectomy for early-stage cervical cancer." Int J Gynecol Cancer **25**(4): 699-706.

OBJECTIVE: Radical vaginal trachelectomy (RVT) offers a possibility for future childbearing for young women with early-stage cervical cancer. However, the literature on quality of life and self-reported morbidity in patients undergoing RVT is scarce. The aim of this study was to prospectively assess quality of life after RVT with focus on urogynecological morbidity and lymphedema. Furthermore, the aim of this study was to compare results with those in women treated with radical abdominal hysterectomy (RAH) and with age-matched control women from the general population. METHODS AND MATERIALS: Eighteen patients with early-stage cervical cancer operated with RVT were prospectively included and assessed preoperatively, 3, 6, and 12 months postoperatively using validated questionnaires. Thirty-two patients treated with RAH were included consecutively and assessed once at 12 months postsurgery, whereas an age-matched control group of 30 healthy women was assessed once. RESULTS: Fifty percent of the RVT group and 41% of the RAH reported any grade of incomplete bladder emptying problems at 1 year postsurgery assessment. Eleven percent of the RVT patients and 12.5% of the RAH patients reported severe lymphedema of the legs as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module. The Global Health Status scores of the RVT patients improved over time but were significantly lower than in the healthy controls during the entire observation time (P = 0.029). CONCLUSIONS: Patients treated with RVT for early-stage cervical cancer had persistent bladder emptying problems and lymphedema comparable to those experienced by patients treated with RAH and significantly higher than those reported by healthy control women.

Froeding, L. P., C. Ottosen, H. Rung-Hansen, D. Svane, B. J. Mosgaard and P. T. Jensen (2014). "Sexual functioning and vaginal changes after radical vaginal trachelectomy in early stage cervical cancer patients: a longitudinal study." J Sex Med **11**(2): 595-604.

INTRODUCTION: Radical vaginal trachelectomy (RVT) offers low complication rate, good survival, and possibility for future childbearing for young women with early stage cervical cancer. However, the literature on quality of life (QOL) and sexual functioning in patients undergoing RVT is scarce. AIM: The aims of this study were to prospectively assess sexual function after RVT and to compare scores of sexual function in patients operated by RVT and radical abdominal hysterectomy (RAH) with those of age-matched control women from the general population. METHODS: Eighteen patients with early stage cervical cancer operated with RVT were prospectively included and assessed preoperatively, and 3, 6, and 12 months postoperatively using validated questionnaires. RAH patients were included consecutively and assessed once at 12 months postsurgery, while an age-matched control group of 30 healthy women was assessed once. MAIN OUTCOME MEASURE: Sexual dysfunction total score as measured by the Female Sexual Function Index (FSFI) was the main outcome measure. RESULTS: During the 12 months posttreatment, RVT patients tended to have persistent sexual dysfunction as measured by FSFI (mean overall score <26.55 at each assessment) and Female Sexual Distress Scale (mean overall score > 11). Sexual worry (P < 0.001) and lack of sexual desire (P = 0.038) were more frequently reported among patients in both treatment groups compared with control women. Sexual activity increased significantly during the observation time for the RVT group (P = 0.023) and reached that of healthy women. Global

Health Status score improved over time for the RVT group but never reached that of healthy control women (P = 0.029). CONCLUSIONS: Our data suggest that patients treated with RVT for early stage cervical cancer experience persistent sexual dysfunction up to one year post surgery influencing negatively on their QOL.

Greimel, E. R., K. Kuljanic Vlasic, A. C. Waldenstrom, V. M. Duric, P. T. Jensen, S. Singer, W. Chie, A. Nordin, V. Bjelic Radisic and D. Wydra (2006). "The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24." Cancer **107**(8): 1812-1822.

BACKGROUND: The authors report on the development and validation of a cervical cancer module for the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life (QoL) questionnaire (QLQ), which was designed to assess disease-specific and treatment-specific aspects of QoL in patients with cervical cancer. METHODS: The cervical cancer module (EORTC QLQ-CX24) was developed in a multicultural, multidisciplinary setting to supplement the EORTC QLQ-C30 core questionnaire. The QLQ-C30 and the cervical cancer module were administered to 346 patients with cervical cancer who underwent radical hysterectomy and received radiotherapy and chemotherapy. Psychometric analyses were performed by using data from 2 independent samples. RESULTS: The QLQ-CX24 consists of 3 multiitem scales and 5 single-item scales. Multitrait scaling analyses revealed high internal consistencies for the subscales with Cronbach alpha coefficients ranging from .72 to .87 (Symptom Experience, .72; Body Image, .86; Sexual/Vaginal Functioning, .87). Convergent and discriminant validity were fulfilled with scaling errors below 3%. The QLQ-CX24 was capable of discriminating between clinical subgroups. All items exhibited good compliance with <3% missing values. Most patients completed the EORTC QLQ-C30 and the QLQ-CX24 in <15 minutes (86%), and many did not require any assistance to complete the questionnaires (65%). CONCLUSIONS: The current psychometric analyses supported the content and construct validity and the reliability of the EORTC QLQ-CX24 module. This newly developed module is a useful instrument for assessing the QoL of patients who are treated for cervical cancer both in clinical trials and in clinical practice.

Holt, K. A., O. Mogensen, P. T. Jensen and D. G. Hansen (2015). "Goal setting in cancer rehabilitation and relation to quality of life among women with gynaecological cancer." Acta Oncol **54**(10): 1814-1823.

BACKGROUND: Rehabilitation should be integrated in the routine cancer care of women treated for gynaecological cancers. Goal setting is expected to facilitate the process through patient involvement and motivation. Our knowledge about goal setting in cancer rehabilitation is, however, sparse. OBJECTIVES: This study aimed to: 1) analyse rehabilitation goals defined during hospital-based rehabilitation in patients with gynaecological cancer, with regard to number, category, changes over time, and differences between cancer diagnosis, and 2) analyse the association between health-related quality of life and goals defined for rehabilitation. MATERIAL AND METHODS: Consecutively, all patients treated surgically for endometrial, ovarian, and cervical cancer were invited for hospital-based rehabilitation at Odense University Hospital, Denmark, including two sessions at the hospital one and three months following surgery and two phone calls for follow-up. Questionnaires from the EORTC were used to prepare patients and facilitate individual goal setting with definitions of up to three goals. All goals were grouped into six categories. RESULTS: A total of 151 (63%) patients accepted the invitation including 50 endometrial, 65 ovarian, and 36 cervical cancers patients. All patients defined goals at the first session, 76.4% defined three goals, 21.9% two, and 1.6% had one goal. Physical goals decreased over time but were the most frequent at both sessions (98% and 89%). At both sessions, the social and emotional categories were the second and third most frequent among patients with endometrial and ovarian cancer. Sexual issues were dominant among the cervical cancer patients. Regression analysis showed significant

association between quality of life scores and goal setting within the social and emotional domains. CONCLUSION: Goal setting seemed feasible in all problem areas. The EORTC questionnaires were helpful during the process although expectations of the sub-scores being predictive of which areas to address were not convincing.

Holt, K. A., O. Mogensen, P. T. Jensen and D. G. Hansen (2015). "Goal setting in cancer rehabilitation and relation to quality of life among women with gynaecological cancer." Acta Oncol **54**(10): 1814-1823.

BACKGROUND: Rehabilitation should be integrated in the routine cancer care of women treated for gynaecological cancers. Goal setting is expected to facilitate the process through patient involvement and motivation. Our knowledge about goal setting in cancer rehabilitation is, however, sparse. OBJECTIVES: This study aimed to: 1) analyse rehabilitation goals defined during hospital-based rehabilitation in patients with gynaecological cancer, with regard to number, category, changes over time, and differences between cancer diagnosis, and 2) analyse the association between health-related quality of life and goals defined for rehabilitation. MATERIAL AND METHODS: Consecutively, all patients treated surgically for endometrial, ovarian, and cervical cancer were invited for hospital-based rehabilitation at Odense University Hospital, Denmark, including two sessions at the hospital one and three months following surgery and two phone calls for follow-up. Questionnaires from the EORTC were used to prepare patients and facilitate individual goal setting with definitions of up to three goals. All goals were grouped into six categories. RESULTS: A total of 151 (63%) patients accepted the invitation including 50 endometrial, 65 ovarian, and 36 cervical cancers patients. All patients defined goals at the first session, 76.4% defined three goals, 21.9% two, and 1.6% had one goal. Physical goals decreased over time but were the most frequent at both sessions (98% and 89%). At both sessions, the social and emotional categories were the second and third most frequent among patients with endometrial and ovarian cancer. Sexual issues were dominant among the cervical cancer patients. Regression analysis showed significant association between quality of life scores and goal setting within the social and emotional domains. CONCLUSION: Goal setting seemed feasible in all problem areas. The EORTC questionnaires were helpful during the process although expectations of the sub-scores being predictive of which areas to address were not convincing.

Jensen, P. T. and L. P. Froeding (2015). "Pelvic radiotherapy and sexual function in women." Transl Androl Urol **4**(2): 186-205.

BACKGROUND: During the past decade there has been considerable progress in developing new radiation methods for cancer treatment. Pelvic radiotherapy constitutes the primary or (neo) adjuvant treatment of many pelvic cancers e.g., locally advanced cervical and rectal cancer. There is an increasing focus on late effects and an increasing awareness that patient reported outcomes (PROs) i.e., patient assessment of physical, social, psychological, and sexual functioning provides the most valid information on the effects of cancer treatment. Following cure of cancer allow survivors focus on quality of life (QOL) issues; sexual functioning has proved to be one of the most important aspects of concern in long-term survivors. METHODS: An updated literature search in PubMed was performed on pelvic radiotherapy and female sexual functioning/dysfunction. Studies on gynaecological, urological and gastrointestinal cancers were included. The focus was on the period from 2010 to 2014, on studies using PROs, on potential randomized controlled trials (RCTs) where female sexual dysfunction (FSD) at least constituted a secondary outcome, and on studies reporting from modern radiotherapy modalities. RESULTS: The literature search revealed a few RCTs with FSD evaluated as a PRO and being a secondary outcome measure in endometrial and in rectal cancer patients. Very limited information could be extracted regarding FSD in bladder, vulva, and anal cancer patients. The literature before and after 2010 confirms that pelvic radiotherapy, independent on modality, increases the risk significantly for FSD both compared

to data from age-matched healthy control women and compared to data on patients treated by surgery only. There was only very limited data available on modern radiotherapy modalities. These are awaited during the next five years. Several newer studies confirm that health care professionals are still reluctant to discuss treatment induced sexual dysfunction with patients. CONCLUSIONS: Pelvic radiotherapy has a persistent deteriorating effect on the vaginal mucosa impacting negatively on the sexual functioning in female cancer patients. Hopefully, modern radiotherapy modalities will cause less vaginal morbidity but results are awaited to confirm this assumption. Health care professionals are encouraged to address potential sexual dysfunction both before and after radiotherapy and to focus more on quality than on quantity.

Jensen, P. T., M. Groenvold, M. C. Klee, I. Thranov, M. A. Petersen and D. Machin (2003). "Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer." Int J Radiat Oncol Biol Phys **56**(4): 937-949.

PURPOSE: To investigate the longitudinal course of self-reported sexual function and vaginal changes in patients disease free after radiotherapy (RT) for locally advanced, recurrent, or persistent cervical cancer. MATERIALS AND METHODS: A total of 118 patients referred for RT were included. The patients were assessed, using a validated self-assessment questionnaire, at the termination of RT and 1, 3, 6, 12, 18, and 24 months later. The results were compared with an age-matched control group from the general population. RESULTS: Persistent sexual dysfunction and adverse vaginal changes were reported throughout the 2 years after RT, with small changes over time: approximately 85% had low or no sexual interest, 35% had moderate to severe lack of lubrication, 55% had mild to severe dyspareunia, and 30% were dissatisfied with their sexual life. A reduced vaginal dimension was reported by 50% of the patients, and 45% were never, or only occasionally, able to complete sexual intercourse. Despite sexual dysfunction and vaginal adverse effects, 63% of those sexually active before having cancer remained sexually active after treatment, although with a considerably decreased frequency. CONCLUSIONS: Patients who are disease free after RT for locally advanced, recurrent, or persistent cervical cancer are at high risk of experiencing persistent sexual and vaginal problems compromising their sexual activity and satisfaction.

Jensen, P. T., M. Groenvold, M. C. Klee, I. Thranov, M. A. Petersen and D. Machin (2004). "Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study." Cancer **100**(1): 97-106.

BACKGROUND: Limited knowledge exists concerning the impact of radical hysterectomy (RH) alone on the sexual function of patients with early-stage cervical carcinoma. The authors investigated the longitudinal course of self-reported sexual function after RH. METHODS: The current study was comprised of 173 patients with lymph node-negative, early-stage cervical carcinoma who had undergone RH and pelvic lymphadenectomy. They were assessed prospectively using a validated self-assessment questionnaire 5 weeks and 3 months, 6 months, 12 months, 18 months, and 24 months after RH. Results were compared with an age-matched control group from the general population. RESULTS: Compared with control women, patients experienced severe orgasmic problems and uncomfortable sexual intercourse due to a reduced vaginal size during the first 6 months after RH, severe dyspareunia during the first 3 months, and sexual dissatisfaction during the 5 weeks after RH. A persistent lack of sexual interest and lubrication were reported throughout the first 2 years after RH. Long-term lack of sexual interest and insufficient vaginal lubrication were confirmed by the patient's self-reported changes 12 months after RH compared with before the cancer diagnosis and by a pre-post comparison within patients. However, most of the patients who were sexually active before their cancer diagnosis were sexually active again 12 months after surgery (91%), although with a decrease in sexual frequency

reported. CONCLUSIONS: RH had a persistent and negative impact on patients' sexual interest and vaginal lubrication whereas the majority of other sexual and vaginal problems disappeared over time. Sexual and vaginal problems in the short-term and long-term after RH should be discussed with the patient before and after surgery.

Jeppesen, M. M., O. Mogensen, P. Dehn and P. T. Jensen (2015). "Needs and priorities of women with endometrial and cervical cancer." J Psychosom Obstet Gynaecol **36**(3): 122-132.

INTRODUCTION: Rehabilitation after cancer is important, and efficient rehabilitation requires knowledge of patient's needs. This study aimed to identify short-term rehabilitation needs of women with endometrial and cervical cancer. METHODS: Ninety-six women (82.6%) were included in an exploratory questionnaire study from Odense University Hospital from September 2011 to March 2012. Needs were assessed pre-treatment and 3 months later using the three-levels-of-needs questionnaire. Furthermore, 16 women participated in focus group interviews following the treatment. The interviews were audio-recorded, transcribed verbatim and analyzed thematically. RESULTS: Forty-four of the included women were diagnosed with cervical cancer (median age 45 years). Of these, 22 had FIGO-stage 1 disease (50%) and 23 received radiation therapy (52.3%). The remaining 52 women (median age 66.5 years) were diagnosed with endometrial cancer. Of these, 38 had FIGO-stage 1 disease (73.1%) and 25 were treated with laparoscopic surgery (48.1%). Emotional functioning was significantly worse prior to treatment in both the cancers ($p < 0.001$ cervical and $p = 0.002$ endometrial) and worry constituted an unmet need in 70.7% of cervical and 34.7% of endometrial cancer patients. Both the patient groups experienced significant lymphedema post-treatment [endometrial cancer ($p = 0.006$) and cervical cancer ($p = 0.002$)]. Further, urological problems were more prevalent post-treatment in endometrial cancer patients ($p = 0.018$), while sexual problems were of specific concern for cervical cancer patients ($p = 0.029$). However, in both cancer groups, the mean problem intensity scores were comparable to normative data, suggesting that the majority of patients will not require extensive rehabilitation. Qualitative analysis indicated that treatment modality and marital status severely impacted on coping, suggesting that irradiated and single women are at higher risk of developing rehabilitation needs. Additionally, women younger than 55 years more often requested help dealing with sexual and psychological complications. DISCUSSION: Women with endometrial and cervical cancer experience emotional problems prior to therapy and lymphedema, and urological and sexual problems following treatment. An awareness of these problems may facilitate early identification of women with unmet needs and enable individualized follow-up adjusted for such patient's needs. Interventions aimed at improving sexual and psychological functioning should be available.

Mark Kane, consultant (US)

Provided by HPV Prevention and Control Board Secretariat:

Bosch, F. X., T. R. Broker, D. Forman, A. B. Moscicki, M. L. Gillison, J. Doorbar, P. L. Stern, M. Stanley, M. Arbyn, M. Poljak, J. Cuzick, P. E. Castle, J. T. Schiller, L. E. Markowitz, W. A. Fisher, K. Canfell, L. A. Denny, E. L. Franco, M. Steben, M. A. Kane, M. Schiffman, C. J. Meijer, R. Sankaranarayanan, X. Castellsague, J. J. Kim, M. Brotons, L. Alemany, G. Albero, M. Diaz and S. de Sanjose (2013). "Comprehensive control of human papillomavirus infections and related diseases." Vaccine **31 Suppl 8**: I1-31.

Infection with human papillomavirus (HPV) is recognized as one of the major causes of infection-related cancer worldwide, as well as the causal factor in other diseases. Strong evidence for a causal etiology with HPV has been stated by the International Agency for Research on Cancer for cancers of the cervix uteri, penis, vulva, vagina, anus and oropharynx (including base of the tongue and tonsils). Of the estimated 12.7 million new cancers occurring in 2008 worldwide, 4.8% were attributable to HPV infection, with substantially higher incidence and mortality rates seen in developing versus developed countries. In recent years, we have gained tremendous knowledge about HPVs and their interactions with host cells, tissues and the immune system; have validated and implemented strategies for safe and efficacious prophylactic vaccination against HPV infections; have developed increasingly sensitive and specific molecular diagnostic tools for HPV detection for use in cervical cancer screening; and have substantially increased global awareness of HPV and its many associated diseases in women, men, and children. While these achievements exemplify the success of biomedical research in generating important public health interventions, they also generate new and daunting challenges: costs of HPV prevention and medical care, the implementation of what is technically possible, socio-political resistance to prevention opportunities, and the very wide ranges of national economic capabilities and health care systems. Gains and challenges faced in the quest for comprehensive control of HPV infection and HPV-related cancers and other disease are summarized in this review. The information presented may be viewed in terms of a reframed paradigm of prevention of cervical cancer and other HPV-related diseases that will include strategic combinations of at least four major components: 1) routine introduction of HPV vaccines to women in all countries, 2) extension and simplification of existing screening programs using HPV-based technology, 3) extension of adapted screening programs to developing populations, and 4) consideration of the broader spectrum of cancers and other diseases preventable by HPV vaccination in women, as well as in men. Despite the huge advances already achieved, there must be ongoing efforts including international advocacy to achieve widespread-optimally universal-implementation of HPV prevention strategies in both developed and developing countries. This article summarizes information from the chapters presented in a special ICO Monograph 'Comprehensive Control of HPV Infections and Related Diseases' Vaccine Volume 30, Supplement 5, 2012. Additional details on each subtopic and full information regarding the supporting literature references may be found in the original chapters.

Bosch, F. X., V. Tsu, A. Vorsters, P. Van Damme and M. A. Kane (2012). "Reframing cervical cancer prevention. Expanding the field towards prevention of human papillomavirus infections and related diseases." Vaccine **30 Suppl 5**: F1-11.

The reframed paradigm of cervical cancer prevention will include strategic combinations of at least four major components: 1) routine introduction of human papillomavirus (HPV) vaccines to women in all countries, 2) extension and simplification of existing screening programs using HPV-based technology, 3) extension of adapted screening programs to developing populations, and 4) consideration of the broader spectrum of cancers and other diseases preventable by HPV vaccination in women, as well as in men. On a global scale, vaccination of newborns and infants is well established and has developed a successful working infrastructure. The hepatitis B virus (HBV) vaccination programs offer a model for HPV

introduction in which newborn and infant immunization achieves a rapid reduction in the prevalence of the HBV carrier rates in immunized cohorts of children, and of liver cirrhosis and liver cancer decades later. In contrast, screening for cervical pre-cancer is largely restricted to industrialized populations and upper social classes in developing countries. The expertise gained by vaccination programs worldwide needs to be coordinated with the traditional cervical cancer prevention community of gynecologists and pathologists. Significant political and advocacy efforts at the Global level (World Health Organization, other United Nations agencies and The GAVI Alliance) need to be organized and reinforced to achieve a meaningful reduction in HPV transmission and its related health conditions and cancers. This desirable goal is now scientifically and technologically attainable, and great progress is being made in obtaining financing for global HPV immunization. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.

Kane, M. A. (2012). "Preventing cancer with vaccines: progress in the global control of cancer." Cancer Prev Res (Phila) **5**(1): 24-29.

The cancer control community is largely unaware of great advances in the control of major human cancers with vaccines, including the dramatic control of hepatocellular (liver) cancer with hepatitis B virus (HBV) vaccine, now used routinely in more than 90% of countries. The biotechnology revolution has given us a new generation of highly effective vaccines against major global killers, global funding for immunization is orders of magnitude higher than ever before, and the vaccine delivery infrastructure has improved very significantly even in the poorest countries. Liver cancer is the greatest cause of cancer deaths in men of sub-Saharan Africa and much of Asia. Even in highly endemic countries such as China, the prevalence of HB surface antigen carriers has fallen from 10% to 1%-2% in immunized cohorts of children, and liver cancer has already fallen dramatically in Taiwanese children. The Global Alliance for Vaccines and Immunization (now called the GAVI Alliance) has greatly expedited this success by providing HBV vaccine free for five years in most of the world's 72 poorest countries. HBV vaccination can serve as a model for the global control of human papillomavirus (HPV)-related cervical and other cancers with HPV vaccines. Cervical cancer is the greatest cause of cancer death in women in many developing countries; HPV vaccines are highly effective in preventing HPV infection and precancerous lesions in women, and the quadrivalent vaccine also prevents genital warts in men and women and precancerous anal lesions in men. HPV is causing a growing proportion of oropharyngeal cancers, and HPV-related noncervical cancers (penile, anal, and oropharyngeal) may exceed the incidence of cervical cancer within a decade in industrial countries, where cervical screening is effective, causing reevaluation of male HPV immunization. In developing countries, few women are screened for cervical precancerous lesions, making immunization even more important. Currently, 26 primarily industrial countries routinely immunize girls with HPV vaccine, and GAVI will begin to accept applications in 2012 to fund vaccine in developing countries that can deliver the vaccine and if GAVI can negotiate an acceptable price (one manufacturer has already offered a price of $5 per dose).

Kane, M. A., B. Serrano, S. de Sanjose and S. Wittet (2012). "Implementation of human papillomavirus immunization in the developing world." Vaccine **30 Suppl 5**: F192-200.

Cervical cancer is the second leading cause of cancer death in women in less developed regions of the world and the leading cause of cancer deaths in GAVI-eligible countries, where 54% of worldwide cervical cancer deaths occur. If prevention is not implemented in these countries, population growth alone will lead to a 63% increase in deaths by 2025. Human papillomavirus (HPV) vaccines are routinely used in the National Immunization Programs in most industrial countries, and the decision by the GAVI Alliance to accept applications from eligible developing countries for HPV vaccine support is the single most important opportunity for children in these countries to be protected against HPV-related

diseases. As it has done for other vaccines, such as Haemophilus influenzae type b, rotavirus and pneumococcal conjugate vaccines, GAVI should strongly consider developing and funding a group dedicated to working on all aspects of HPV vaccine introduction in the developing world. Immunization in middle-income developing countries not eligible for GAVI support will depend on "tiered" pricing policies or regional procurement schemes to make vaccine available at prices significantly lower than those in industrial countries. Immunization coverage of infants has reached high levels in many of the poorest developing countries where complementary strategies for HPV control, such as adult screening and treatment, are poorly developed. Immunizing young adolescents will require expansion of immunization infrastructure to reach cohorts that currently are largely unreached, but the success of school-based strategies in industrial countries and developing country demonstration projects provides hope that relatively high coverage may be achieved in many countries. Communication and advocacy strategies for HPV control need to carefully consider local cultural attitudes toward HPV-related issues. Current strategies supported by health economic analyses call for female only immunization, but concerns have been expressed as to whether this is the optimal strategy for the developing world. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.

Heffernan, M. E., S. M. Garland and M. A. Kane (2010). "Global reduction of cervical cancer with human papillomavirus vaccines: insights from the hepatitis B virus vaccine experience." Sex Health **7**(3): 383-390.

BACKGROUND: Worldwide, prophylactic vaccines against two major human cancers are now commercially available: hepatitis B virus (HBV) vaccines (first licensed in 1982) against primary hepatocellular carcinoma and human papillomavirus (HPV) vaccines (first licensed 2006) against cervical cancer. Initial implementation strategies for HBV vaccination were not successful in preventing disease in the community: it took 15 years for significant global reduction in the burden of this disease. METHODS: We compare and contrast HBV vaccine experiences to challenges for successful global HPV vaccination strategies, and make recommendations accordingly. RESULTS: Lessons from HBV immunisation for successful outcomes with HPV immunisation showed that several factors need to be met: (i) the engagement of key stakeholders in all aspects of planning and delivery of HPV vaccine strategies; (ii) understanding the specific characteristics of targeted population groups; (iii) global cooperation and support with WHO recommendations; (iv) Government supported mass immunization programs and cooperation between public and private entities; (v) affordable HPV vaccines for some regions; (vi) culturally appropriate and diverse public education programs in targeted health promotion strategies; (vii) pro-active health providers and parents in encouraging adolescents to undertake HPV vaccination; and (vii) eventual immunisation of infants. CONCLUSIONS: The key to success will be affordable, readily deliverable HPV vaccines to young girls as universal campaigns.

Kane, M. A. (2010). "Global implementation of human papillomavirus (HPV) vaccine: lessons from hepatitis B vaccine." Gynecol Oncol **117**(2 Suppl): S32-35.

Development of safe and effective vaccines against human papillomavirus (HPV)-the second vaccine against a major human cancer-is one of the most important medical and public health achievements of this century. As with all new vaccines, HPV is currently expensive and this cost precludes its use in the developing world, which has the greatest burden of disease from HPV-related cancers. Hepatitis B (HB) virus vaccine, which prevents chronic HB infection and related cirrhosis and liver cancer, has been successfully introduced as a routine vaccine for children in 89% of countries, including the poorest. The success of this vaccine provides a model for the introduction of HPV vaccine and control of cervical and other HPV-related cancers and genital warts. Lessons learned from HB vaccine introduction are relevant to our efforts to introduce HPV vaccine globally. As with HB vaccine, introduction of HPV vaccine into national immunization programs and routine use of this vaccine, funded by governments, will

be needed to control HPV-related disease on a global basis. Global funding support will be needed to make control a reality for the poorest countries, and the program to accomplish this, the Global Alliance for Vaccines and Immunization (GAVI), has already expressed great interest in including HPV vaccine. For this to occur, the manufacturers will need to dramatically reduce the vaccine price for the poorest developing countries, and tier prices for wealthier developing countries not eligible for GAVI support. Countries will need to decide on the priority of HPV control in the context of other important new vaccines against pneumococcal pneumonia and rotavirus diarrhea.

Kane, M. A. (2008). "Human papillomaviruses (HPV) vaccines: implementation and communication issues." J Fam Plann Reprod Health Care **34**(1): 3-4.

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Rebolj M, Bonde J, Preisler S, Ejegod D, Rygaard C, Lynge E. (2016). "Differential detection of Human Papillomavirus genotypes and cervical intraepithelial neoplasia by four commercial assays." J Clin Microbiol : 01321-16.

Laboratories can nowadays choose from >100 Human Papillomavirus (HPV) assays for cervical screening. Our previous analysis based on the data from the Danish Horizon study, however, showed that four widely used assays, Hybrid Capture 2 (HC2), cobas, CLART and APTIMA, frequently do not detect the same HPV infections. Here, we determined the characteristics of the concordant (all four assays returning a positive HPV test result) and discordant samples (all other HPV-positive samples) in primary cervical screening at 30-65 years (n=2859) and in a concurrent referral population from the same catchment area (n=885). HPV testing followed the manufacturers' protocols. Women with abnormal cytology were managed according to the routine recommendations. Cytology-normal/HPV-positive women were invited for repeated testing in 18 months. Screening history and histologically confirmed cervical intraepithelial neoplasia (CIN) in 2.5 years after the baseline testing were determined from the national pathology register. HPV-positive women undergoing primary screening having concordant samples were more likely to harbor high-risk infections and less likely to harbor only low-risk infections than women with discordant samples. Additionally, assay signal strengths were substantially higher in concordant samples. More than 80% of ≥CIN2 were found in women with concordant samples, and none where the infection was detected by only one assay. These patterns were similar in the referral population, despite the younger age and more HPV infections. HPV test result discordance identified a cluster of low-risk HPV infections that were hardly ever associated with high-grade CIN and, almost exclusively, represented false-positive screening findings.

Hestbech MS, Lynge E, Kragstrup J, Siersma V, Vazquez-Prada Baillet M, Brodersen J. (2015). "The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark." BMJ Open.**5**(8):e007921.

Frederiksen ME, Baillet MV, Dugué PA, Jensen PT, Rygaard C, Hallas J, Lynge E. (2015). "Abnormal cervical cytology and health care use: a population-based register study." Gynecol Oncol **139**(1):63-9.

Sander BB, Vázquez-Prada M, Rebolj M, Valentiner-Branth P, Lynge E. (2015). "Mothers' and their daughters' use of preventive measures against cervical cancer." Scand J Public Health **43**(4):415-22.

Lynge E, Rygaard C, Baillet MV, Dugué PA, Sander BB, Bonde J, Rebolj M. (2014). "Cervical cancer screening at crossroads." APMIS **122**(8):667-73. Review.

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Barloese, M. C., J. Mehlsen, L. Brinth, H. I. Lundberg, P. J. Jennum and R. H. Jensen (2015). "Reduced Baroreflex Sensitivity in Cluster Headache Patients." Headache **55**(6): 815-824.

OBJECTIVE AND BACKGROUND: Important elements of cluster headache (CH) pathophysiology may be seated in the posterior hypothalamus. Cranial autonomic features are inherent, but involvement of systemic autonomic control is still debated. We aimed to characterize autonomic function as investigated by baroreflex sensitivity (BRS) in CH patients. METHODS: Twenty-six active CH patients and an equal number of age-, sex-, and BMI-matched controls underwent head-up tilt table test and BRS was determined by the sequence method. RESULTS: Compared with controls, patients exhibited a blunted reactivity of RR intervals in response to falls and increases in systolic blood pressure (SBP) (15.3 vs. 20.0 ms/mmHg, P = .0041) in the supine position. Also, compared with controls, BRS was lower in patients having suffered an attack within the past 12 hours (n = 13, 12.5 vs. 22.3 ms/mmHg, P = .0091), opposed to those patients who had not (n = 13, 16.0 ms/mmHg, P = .1523). In the tilted position, the drop in SBP at the carotid sinuses was higher in patients who had recently suffered an attack. Despite this, they exhibited a less marked shortening of RR intervals when compared with patients who had been attack free for longer. CONCLUSIONS: CH patients exhibit a subclinical blunting of BRS that may be affected by the attacks themselves. The fast RR interval fluctuations used in this method reflects cardiovagal responses, thus the blunted responses are suggestive of dysfunction in the parasympathetic division of the autonomic nervous system or in the central relay of impulses from the baroreceptors.

Brinth, L., K. Pors and J. Mehlsen (2015). "[Postural orthostatic tachycardia syndrome]." Ugeskr Laeger **177**(18): 853-856.

Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous condition of dysautonomia and suspected autoimmunity characterized by abnormal increments in heart rate upon assumption of the upright posture accompanied by symptoms of cerebral hypoperfusion and sympathoexcitation. An increase in heart rate equal to or greater than 30 bpm or to levels higher than 120 bpm during a head-up tilt test is the main diagnostic criterion. Management includes both non-pharmacological and pharmacological treatment focusing on stress management, volume expansion and heart rate control.

Brinth, L., A. C. Theibel, K. Pors and J. Mehlsen (2015). "Suspected side effects to the quadrivalent human papilloma vaccine." Dan Med J **62**(4): A5064.

Brinth, L. S., K. Pors, A. C. Theibel and J. Mehlsen (2015). "Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus." Vaccine **33**(22): 2602-2605.

Jans, O., L. Brinth, H. Kehlet and J. Mehlsen (2015). "Decreased heart rate variability responses during early postoperative mobilization--an observational study." BMC Anesthesiol **15**: 120.

BACKGROUND: Intact orthostatic blood pressure regulation is essential for early mobilization after surgery. However, postoperative orthostatic hypotension and intolerance (OI) may delay early ambulation. The mechanisms of postoperative OI include impaired vasopressor responses relating to postoperative autonomic dysfunction. Thus, based on a previous study on haemodynamic responses during mobilization before and after elective total hip arthroplasty (THA), we performed secondary analyses of heart rate variability (HRV) and aimed to identify possible abnormal postoperative autonomic responses in relation to postural change. METHODS: A standardized mobilization protocol before, 6 and

24 h after surgery was performed in 23 patients scheduled for elective THA. Beat-to-beat arterial blood pressure was measured by photoplethysmography and HRV was derived from pulse wave interbeat intervals and analysed in the time and frequency domain as well as by non-linear analysis using sample entropy RESULTS: Before surgery, arterial pressures and HR increased upon standing, while HRV low (LF) and high frequency (HF) components remained unchanged. At 6 and 24 h after surgery, resting total HRV power, sample entropy and postural responses in arterial pressures decreased compared to preoperative conditions. During standing HF variation increased by 16.7 (95 % CI 8.0-25.0) normalized units (nu) at 6 h and 10.7 (2.0-19.4) nu at 24 h compared to the preoperative evaluation. At 24 h the LF/HF ratio decreased from 1.8 (1.2-2.6) nu when supine to 1.2 (0.8-1.8) nu when standing. CONCLUSIONS: This study observed postoperative autonomic cardiovascular dysregulation that may contribute to limited HRV responses during early postoperative mobilization. TRIAL REGISTRATION: ClinicalTrials.gov NCT01089946.

Jans, O., J. Mehlsen, P. Kjaersgaard-Andersen, H. Husted, S. Solgaard, J. Josiassen, T. H. Lunn and H. Kehlet (2015). "Oral Midodrine Hydrochloride for Prevention of Orthostatic Hypotension during Early Mobilization after Hip Arthroplasty: A Randomized, Double-blind, Placebo-controlled Trial." Anesthesiology **123**(6): 1292-1300.

BACKGROUND: Early postoperative mobilization is essential for rapid recovery but may be impaired by orthostatic intolerance (OI) and orthostatic hypotension (OH), which are highly prevalent after major surgery. Pathogenic mechanisms include an insufficient postoperative vasopressor response. The oral alpha-1 agonist midodrine hydrochloride increases vascular resistance, and the authors hypothesized that midodrine would reduce the prevalence of OH during mobilization 6 h after total hip arthroplasty relative to placebo. METHODS: This double-blind, randomized trial allocated 120 patients 18 yr or older and scheduled for total hip arthroplasty under spinal anesthesia to either 5 mg midodrine hydrochloride or placebo orally 1 h before mobilization at 6 and 24 h postoperatively. The primary outcome was the prevalence of OH (decrease in systolic or diastolic arterial pressures of > 20 or 10 mmHg, respectively) during mobilization 6 h after surgery. Secondary outcomes were OI and hemodynamic responses to mobilization at 6 and 24 h. RESULTS: At 6 h, 14 (25%; 95% CI, 14 to 38%) versus 23 (39.7%; 95% CI, 27 to 53%) patients had OH in the midodrine and placebo group, respectively, relative risk 0.63 (0.36 to 1.10; P = 0.095), whereas OI was present in 15 (25.0%; 15 to 38%) versus 22 (37.3%; 25 to 51%) patients, relative risk 0.68 (0.39 to 1.18; P = 0.165). At 24 h, OI and OH prevalence did not differ between groups. CONCLUSIONS: Preemptive use of oral 5 mg midodrine did not significantly reduce the prevalence of OH during early postoperative mobilization compared with placebo. However, further studies on dose and timing are warranted since midodrine is effective in chronic OH conditions.

Janum, S., S. T. Nielsen, M. U. Werner, J. Mehlsen, H. Kehlet and K. Moller (2016). "Pain perception in healthy volunteers: effect of repeated exposure to experimental systemic inflammation." Innate Immun **22**(7): 546-556.

We aimed to study the relationship between pain perception and cytokine release during systemic inflammation. We present a randomized crossover trial in healthy volunteers (n = 17) in 37 individual trials. Systemic inflammation was induced by an i.v. bolus of Escherichia coli LPS (2 ng/kg) on two separate trial days, with or without a nicotine patch applied 10 h previously. Pain perception at baseline, and 2 and 6 h after LPS was assessed by pressure algometry and tonic heat stimulation at an increasing temperature (45-48) during both trials. Compared with baseline, pain pressure threshold was reduced 2 and 6 h after LPS, while heat pain perception was accentuated at all testing temperatures after 2 but not 6 h. The magnitude of changes in pain perception did not correlate to cytokine release. No effect of transdermal nicotine or training status was observed. In conclusion, LPS administration in healthy human volunteers leads to reduction in pain pressure threshold and an increase in pain perception to heat stimuli, supporting a relationship between acute systemic inflammation and pain perception.

Joura, E. A., A. R. Giuliano, O. E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, E. D. Moreira, Jr., Y. Ngan, L. K. Petersen, E. Lazcano-Ponce, P. Pitisuttithum, J. A. Restrepo, G. Stuart, L. Woelber, Y. C. Yang, J. Cuzick, S. M. Garland, W. Huh, S. K. Kjaer, O. M. Bautista, I. S. Chan, J. Chen, R. Gesser, E. Moeller, M. Ritter, S. Vuocolo and A. Luxembourg (2015). "A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women." N Engl J Med **372**(8): 711-723.

Kosalaraksa, P., J. Mehlsen, T. Vesikari, A. Forsten, K. Helm, P. Van Damme, E. A. Joura, K. Ciprero, R. Maansson, A. Luxembourg and A. Sobanjo-ter Meulen (2015). "An open-label, randomized study of a 9-valent human papillomavirus vaccine given concomitantly with diphtheria, tetanus, pertussis and poliomyelitis vaccines to healthy adolescents 11-15 years of age." Pediatr Infect Dis J **34**(6): 627-634.

Riberholt, C. G., N. D. Olesen, M. Thing, C. B. Juhl, J. Mehlsen and T. H. Petersen (2016). "Impaired Cerebral Autoregulation during Head Up Tilt in Patients with Severe Brain Injury." PLoS One **11**(5): e0154831.

Early mobilization is of importance for improving long-term outcome for patients after severe acquired brain injury. A limiting factor for early mobilization by head-up tilt is orthostatic intolerance. The purpose of the present study was to examine cerebral autoregulation in patients with severe acquired brain injury and a low level of consciousness. Fourteen patients with severe acquired brain injury and orthostatic intolerance and fifteen healthy volunteers were enrolled. Blood pressure was evaluated by pulse contour analysis, heart rate and RR-intervals were determined by electrocardiography, middle cerebral artery velocity was evaluated by transcranial Doppler, and near-infrared spectroscopy determined frontal lobe oxygenation in the supine position and during head-up tilt. Cerebral autoregulation was evaluated as the mean flow index calculated as the ratio between middle cerebral artery mean velocity and estimated cerebral perfusion pressure. Patients with acquired brain injury presented an increase in mean flow index during head-up tilt indicating impaired autoregulation ($P < 0.001$). Spectral analysis of heart rate variability in the frequency domain revealed lower magnitudes of ~0.1 Hz spectral power in patients compared to healthy controls suggesting baroreflex dysfunction. In conclusion, patients with severe acquired brain injury and orthostatic intolerance during head-up tilt have impaired cerebral autoregulation more than one month after brain injury.

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Molbak, K., N. D. Hansen and P. Valentiner-Branth (2016). "Pre-Vaccination Care-Seeking in Females Reporting Severe Adverse Reactions to HPV Vaccine. A Registry Based Case-Control Study." PLoS One 11(9): e0162520.

Widgren, K., J. Simonsen, P. Valentiner-Branth and K. Molbak. (2011). "Uptake of the human papillomavirus-vaccination within the free-of-charge childhood vaccination programme in Denmark." Vaccine **29**(52): 9663-9667.

Christian Munk, Danish Cancer Society (Denmark)

Svahn, M. F., C. Munk, T. S. Nielsen, C. von Buchwald, K. Frederiksen and S. K. Kjaer (2016). "Trends in all-cause five-year mortality after head and neck cancers diagnosed over a period of 33 years. Focus on estimated degree of association with human papillomavirus." Acta Oncol **55**(9-10): 1084-1090.

BACKGROUND: Factors influencing survival after head and neck cancer (HNC) include among others stage, age, and sex. More recently, human papillomavirus (HPV) positivity has been described as a favorable prognostic factor in relation to some HNCs. MATERIAL AND METHODS: In this nationwide register-based cohort study of all 20 925 individuals diagnosed with squamous cell carcinoma of the head and neck (HNSCC) in Denmark 1978-2010, we investigate secular trends in all-cause five-year mortality after HNSCC according to the anticipated degree of association with HPV using a Cox proportional hazards model. Furthermore, we examine whether any trend over time differed according to sex, stage, and age at diagnosis. RESULTS: All-cause five-year mortality after HNSCC has decreased over time. The greatest decrease was seen in the last decade (2000-2010) among patients with HNSCC at sites estimated to be strongly associated with HPV, i.e. the base of the tongue and the tonsils, where a 28% decrease per five years (e.g. HRbase of tongue/tonsils=0.72; 95% CI 0.64-0.81) was observed. When examining sex- and age-specific time trends, the decrease in mortality was most pronounced among male patients and patients below 60 years at diagnosis. In contrast, no clear pattern was observed when examining five-year all-cause mortality trends according to stage. CONCLUSION: All-cause five-year mortality after HNSCC has decreased significantly in Denmark from 1978 to 2010, especially for HNSCCs at sites anticipated to be strongly associated with HPV, possibly due to an increasing proportion of HPV-positive HNSCCs.

Manawapat-Klopfer, A., L. T. Thomsen, P. Martus, C. Munk, R. Russ, H. Gmuender, K. Frederiksen, J. Haedicke-Jarboui, F. Stubenrauch, S. K. Kjaer and T. Iftner (2016). "TMEM45A, SERPINB5 and p16INK4A transcript levels are predictive for development of high-grade cervical lesions." Am J Cancer Res **6**(7): 1524-1536.

Women persistently infected with human papillomavirus (HPV) type 16 are at high risk for development of cervical intraepithelial neoplasia grade 3 or cervical cancer (CIN3+). We aimed to identify biomarkers for progression to CIN3+ in women with persistent HPV16 infection. In this prospective study, 11,088 women aged 20-29 years were enrolled during 1991-1993, and re-invited for a second visit two years later. Cervical cytology samples obtained at both visits were tested for HPV DNA by Hybrid Capture 2 (HC2), and HC2-positive samples were genotyped by INNO-LiPA. The cohort was followed for up to 19 years via a national pathology register. To identify markers for progression to CIN3+, we performed microarray analysis on RNA extracted from cervical swabs of 30 women with persistent HPV16-infection and 11 HPV-negative women. Six genes were selected and validated by quantitative PCR. Three genes were subsequently validated within a different and large group of women from the same cohort. Secondly, Kaplan-Meier and Cox-regression analyses were used to investigate whether expression levels of those three genes predict progression to CIN3+. We found that high transcript levels of TMEM45A, SERPINB5 and p16INK4a at baseline were associated with increased risk of CIN3+ during follow-up. The hazard ratios of CIN3+ per 10-fold increase in baseline expression level were 1.6 (95% CI: 1.1-2.3) for TMEM45A, 1.6 (95% CI: 1.1-2.5) for p16INK4a, and 1.8 (95% CI: 1.2-2.7) for SERPINB5. In conclusion, high mRNA expression levels of TMEM45A, SERPINB5 and p16INK4a were associated with increased risk of CIN3+ in persistently HPV16-infected women.

Olesen, T. B., J. Mwaiselage, T. Iftner, C. Kahesa, V. Rasch, K. Frederiksen, C. Munk and S. K. Kjaer (2016). "Risk factors for genital human papillomavirus among men in Tanzania." J Med Virol.

The objective of the study was to assess risk factors for Human Papillomavirus (HPV) among men

in Tanzania, both overall and in relation to HIV status. In a cross-sectional study conducted among 1,813 men in Tanzania, penile swabs were tested for HPV using Hybrid Capture 2 (HC2). Study participants were offered HIV testing. Risk factors for HPV (HC2 high-risk and/or low-risk positivity) were assessed using logistic regression with adjustment for age, lifetime number of sexual partners, and HIV status. Altogether, 372 men (20.5%) were HPV-positive. Among men tested for HIV (n = 1,483), the HIV prevalence was 9.4%. The odds ratio (OR) of HPV increased with increasing age. HIV-positivity was associated with an increased odds ratio of HPV (OR = 1.91; 95%CI: 1.30-2.82), whereas the odds of HPV tended to be lower in circumcised men than in uncircumcised men (OR = 0.77; 95%CI: 0.54-1.09). When stratifying by HIV status, we found lower odds of HPV in overweight HIV-positive men (BMI > 25) than in normal weight HIV-positive men (OR = 0.25; 95%CI: 0.08-0.78). This did not apply to HIV-negative men. Circumcision tended to decrease the odds of HPV both in HIV-positive men and in HIV-negative men, although not being statistically significant. In conclusion, HIV is a strong risk factor for HPV among men in Tanzania. Additionally, in HIV-positive men a high BMI seems to be associated with a lower risk of HPV. Finally, we observed a tendency toward a lower risk of HPV both among HIV-positive and HIV-negative circumcised men compared to their uncircumcised counterparts.

Svahn, M. F., C. Munk, C. von Buchwald, K. Frederiksen and S. K. Kjaer (2016). "Burden and incidence of human papillomavirus-associated cancers and precancerous lesions in Denmark." Scand J Public Health **44**(6): 551-559.

Svahn, M. F., C. Munk, S. M. Jensen, C. von Buchwald, K. Frederiksen and S. K. Kjaer (2016). "Risk of head-and-neck cancer following a diagnosis of severe cervical intraepithelial neoplasia: a nationwide population-based cohort study in Denmark." Gynecol Oncol **142**(1): 128-132.

OBJECTIVE: Women with a history of cervical intraepithelial neoplasia grade 3 including adenocarcinoma in situ (CIN3/AIS) may be more prone to develop cancers of the ano-genital region and head-and-neck cancers. The current literature is, however, limited. METHODS: We established a nationwide cohort of approximately 2,500,000 Danish women born in 1918-1990. By linking the cohort to population-based health registries, we obtained information on CIN3/AIS, cancer, migration, death, education, and smoking. Cox proportional hazards models were used to estimate hazard ratios (HRs) and confidence intervals (CIs) for the association between CIN3/AIS and risk of head-and-neck squamous cell carcinoma (HNSCC). HRs were presented for any HNSCC and for four subgroups categorized by their anticipated degree of association with human papillomavirus (HPV). RESULTS: A history of CIN3/AIS was significantly associated with an increased overall relative risk of HNSCC after adjustment for year of birth, attained age, and length of education. The risk was especially high for sites anticipated to be strongly associated with HPV (e.g. base of tongue, tonsils) (HR, 2.49; 95% CI, 1.84-3.36). Lower risks were found for sites anticipated to be not or weakly associated with HPV (e.g. nasal cavity, middle ear, sinuses) (HR, 1.29; 95% CI, 0.61-2.76). CONCLUSION: Women with a history of CIN3/AIS have a significantly higher risk of HNSCC than women without such a history. The increased relative risk persisted for at least 20years after the CIN3/AIS diagnosis. Women with CIN3/AIS may be more susceptible to the consequences of HPV and/or may have higher risk behavior, such as smoking.

Thomsen, L. T., M. Nygard, S. Stensen, B. Terning Hansen, L. Arnheim Dahlstrom, K. L. Liaw, C. Munk and S. K. Kjaer (2016). "Awareness of human papillomavirus after introduction of HPV vaccination: a large population-based survey of Scandinavian women." Eur J Cancer Prev.

Stensen, S., S. K. Kjaer, S. M. Jensen, K. Frederiksen, J. Junge, T. Iftner and C. Munk (2016). "Factors associated with type-specific persistence of high-risk human papillomavirus infection: A population-based study." Int J Cancer **138**(2): 361-368.

Persistent genital infection with high-risk (HR) human papillomavirus (HPV) is a prerequisite for cervical cancer development. The aim of this study was to identify factors associated with type-specific persistence of HR HPV infections. From a population-based cohort of 40,399 women participating in cervical cancer screening established during 2002-2005, we selected all HR HPV-positive women (N = 7,778). During follow-up (2005-2008), we collected cervical samples from these women and tested them for HPV DNA to determine type-specific HR HPV persistence in the interval 1-4.5 years after enrolment. Data on hospitalisations, prescriptions and socioeconomic factors were obtained from nationwide registers. Women with abnormal cytology at baseline or who had undergone conisation during follow-up were excluded. Factors associated with persistence were identified by logistic regression analysis. The overall rate of HR HPV persistence was 31.4%. The risk for persistence was significantly increased among women with a previous episode of genital warts (OR, 1.35; 95% CI, 1.04-1.74), current use of oral contraceptives (OR, 1.35; 95% CI, 1.13-1.63) or use of systemic glucocorticoids (OR, 2.04; 95% CI, 1.16-3.56). The number of pregnancies or births or use of a hormonal intrauterine device, hormonal therapy or nonsteroidal anti-inflammatory drugs was not associated with risk for HR HPV persistence. A history of genital warts and current use of oral contraceptives or systemic glucocorticoids increased the risk, potentially indicating a decreased immune response to HPV infection. These findings suggest that host immune response characteristics are important in HR HPV persistence and consequently in cervical cancer development.

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Baldur-Felskov, B., C. Munk, T. S. Nielsen, C. Dehlendorff, B. Kirschner, J. Junge and S. K. Kjaer (2015). "Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012." Cancer Causes Control 26(8): 1105-1116.

Garland, S. M., S. K. Kjaer, N. Munoz, S. L. Block, D. R. Brown, M. J. DiNubile, B. R. Lindsay, B. J. Kuter, G. Perez, G. Dominiak-Felden, A. J. Saah, R. Drury, R. Das and C. Velicer (2016). "Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience." Clin Infect Dis 63(4): 519-527.

Prophylactic human papillomavirus (HPV) vaccination programs constitute major public health initiatives worldwide. We assessed the global effect of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease. PubMed and Embase were systematically searched for peer-reviewed articles from January 2007 through February 2016 to identify observational studies reporting the impact or effectiveness of 4vHPV vaccination on infection, anogenital warts, and cervical cancer or precancerous lesions. Over the last decade, the impact of HPV vaccination in real-world settings has become increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake. Maximal reductions of approximately 90% for HPV 6/11/16/18 infection, approximately 90% for genital warts, approximately 45% for low-grade cytological cervical abnormalities, and approximately 85% for high-grade histologically proven cervical abnormalities have been reported. The full public health potential of HPV vaccination is not yet realized. HPV-related disease remains a significant source of morbidity and mortality in developing and developed nations, underscoring the need for HPV vaccination programs with high population coverage.

Garnaes, E., K. Kiss, L. Andersen, M. H. Therkildsen, M. B. Franzmann, B. Filtenborg-Barnkob, E. Hoegdall, C. B. Lajer, E. Andersen, L. Specht, L. Joenson, K. Frederiksen, L. Friis-Hansen, F. C. Nielsen, S. K. Kjaer, B. Norrild and C. von Buchwald (2015). "Increasing incidence of base of tongue cancers from 2000 to 2010 due to HPV: the largest demographic study of 210 Danish patients." Br J Cancer 113(1): 131-134.

Hebnes, J. B., C. Munk, B. Nohr, A. Nielsen, H. O. Jorgensen, T. Iftner and S. K. Kjaer (2015). "Human Papillomavirus Infection Among 2460 Men in Denmark: Prevalence in Relation to Age Using 2 Human Papillomavirus DNA Testing Methods." Sex Transm Dis 42(8): 463-467.

Kjaer, S. K., K. Frederiksen, C. Munk and T. Iftner (2010). "Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence." J Natl Cancer Inst 102(19): 1478-1488.

Kjaer, S. K., C. Munk, J. Junge and T. Iftner (2014). "Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention?" Cancer Causes Control 25(2): 179-189.

Stensen, S., S. K. Kjaer, S. M. Jensen, K. Frederiksen, J. Junge, T. Iftner and C. Munk (2016). "Factors associated with type-specific persistence of high-risk human papillomavirus infection: A population-based study." Int J Cancer 138(2): 361-368.

Persistent genital infection with high-risk (HR) human papillomavirus (HPV) is a prerequisite for cervical cancer development. The aim of this study was to identify factors associated with type-specific persistence of HR HPV infections. From a population-based cohort of 40,399 women participating in

cervical cancer screening established during 2002-2005, we selected all HR HPV-positive women (N = 7,778). During follow-up (2005-2008), we collected cervical samples from these women and tested them for HPV DNA to determine type-specific HR HPV persistence in the interval 1-4.5 years after enrolment. Data on hospitalisations, prescriptions and socioeconomic factors were obtained from nationwide registers. Women with abnormal cytology at baseline or who had undergone conisation during follow-up were excluded. Factors associated with persistence were identified by logistic regression analysis. The overall rate of HR HPV persistence was 31.4%. The risk for persistence was significantly increased among women with a previous episode of genital warts (OR, 1.35; 95% CI, 1.04-1.74), current use of oral contraceptives (OR, 1.35; 95% CI, 1.13-1.63) or use of systemic glucocorticoids (OR, 2.04; 95% CI, 1.16-3.56). The number of pregnancies or births or use of a hormonal intrauterine device, hormonal therapy or nonsteroidal anti-inflammatory drugs was not associated with risk for HR HPV persistence. A history of genital warts and current use of oral contraceptives or systemic glucocorticoids increased the risk, potentially indicating a decreased immune response to HPV infection. These findings suggest that host immune response characteristics are important in HR HPV persistence and consequently in cervical cancer development.

Svahn, M. F., C. Munk, C. von Buchwald, K. Frederiksen and S. K. Kjaer (2016). "Burden and incidence of human papillomavirus-associated cancers and precancerous lesions in Denmark." Scand J Public Health 44(6): 551-559.

Thomsen, L. T., C. Dehlendorff, J. Junge, M. Waldstrom, D. Schledermann, K. Frederiksen and S. K. Kjaer (2016). "Human papillomavirus mRNA and DNA testing in women with atypical squamous cells of undetermined significance: A prospective cohort study." Int J Cancer 139(8): 1839-1850.

In this prospective cohort study, we compared the performance of human papillomavirus (HPV) mRNA and DNA testing of women with atypical squamous cells of undetermined significance (ASC-US) during cervical cancer screening. Using a nationwide Danish pathology register, we identified women aged 30-65 years with ASC-US during 2005-2011 who were tested for HPV16/18/31/33/45 mRNA using PreTect HPV-Proofer (n = 3,226) or for high-risk HPV (hrHPV) DNA using Hybrid Capture 2 (HC2) (n = 9,405) or Linear Array HPV-Genotyping test (LA) (n = 1,533). Women with >/=1 subsequent examination in the register (n = 13,729) were followed for up to 9.5 years for high-grade cervical intraepithelial neoplasia (CIN) or cancer. After 3 years' follow-up, mRNA testing had higher specificity for CIN3 or worse (CIN3+) than HC2 testing (88.1% [95% confidence interval (CI): 86.8-89.6%] versus 59.3% [95% CI: 58.1-60.4%]) and higher positive predictive value (PPV) (38.2% [95% CI: 33.8%-43.1%] versus 19.5% [95% CI: 17.8-20.9%]). However, the sensitivity of mRNA testing was lower than that of HC2 testing (66.7% [95% CI: 59.3-74.5%] versus 97.0% [95% CI: 95.5-98.4%]), and women testing mRNA negative had higher 3-year risk for CIN3+ than those testing HC2 negative (3.2% [95% CI: 2.2-4.2%] versus 0.5% [95% CI: 0.3-0.7%]). Patterns were similar after 18 months and 5 years'; follow-up; for CIN2+ and cancer as outcomes; across all age groups; and when comparing mRNA testing to hrHPV DNA testing using LA. In conclusion, the HPV16/18/31/33/45 mRNA test is not optimal for ASC-US triage due to its low sensitivity and the substantial risk for precancer following a negative test.

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Callreus T, Svanstrom H, Nielsen NM, Poulsen S, Valentiner-Branth P, Hviid A. (2009). "Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events." Vaccine **27**(22):2954-8.

Determining incidence rates of potential adverse events before and after an immunisation programme is initiated, provides a useful framework for the evaluation of vaccine safety concerns. Human papillomavirus vaccination (HPV) of adolescent girls has recently been introduced in Denmark. Using a nationwide hospitalisation registry we estimated incidence rates of immune-mediated disorders before HPV vaccination in a cohort of 418,289 Danish girls aged 12-15 years. We further estimated the expected number of cases of immune-mediated disorders occurring in temporal relationship to a hypothetical HPV vaccination schedule purely by chance. Our results and analytical approach provides a framework for the evaluation of adverse event reports following immunisation of adolescent girls.

Folkenberg M, Callreus T, Svanstrom H, Valentiner-Branth P, Hviid A. (2011). "Spontaneous reporting of adverse events following immunisation against pandemic influenza in Denmark. November 2009-March 2010." Vaccine **29**(6):1180-4.

Our study reviews the spontaneous reports of adverse events following immunisation submitted to the Danish Medicines Agency during the 2009-2010 influenza A/H1N1v season. During the study period (4 November 2009-31 March 2010), 607 reports comprising 1885 adverse events were reported among 339,507 influenza A/H1N1v vaccinated individuals (reporting rate, 179 per 100,000 vaccinated). The majority of individual case safety reports (85%) were submitted by physicians and other health care professionals and concerned known and non-serious reactions occurring within 1 day of vaccination (82%). Events of special interest as defined by EMA prior to vaccination campaign start, comprised 1% of all events. In conclusion, we did not observe any strong signals of any unknown or serious adverse events associated with influenza A/H1N1v vaccination in Denmark. Our experience also demonstrates the well-known limitations of spontaneous reports with respect to evaluation of a casual relationship and highlights the importance for a timely availability of background events rates and the need for new approaches to study late adverse effects following immunisation.

Sander BB, Rebolj M, Valentiner-Branth P, Lynge E. (2012). "Introduction of human papillomavirus vaccination in Nordic countries." Vaccine **30**(8):1425-33.

INTRODUCTION: Cervical screening has helped decrease the incidence of cervical cancer, but the disease remains a burden for women. Human Papillomavirus (HPV) vaccination is now a promising tool for control of cervical cancer. Nordic countries (Denmark, Finland, Greenland, Iceland, Norway and Sweden) are relatively wealthy with predominantly publicly paid health care systems. The aim of this paper was to provide an update of the current status of introduction of HPV vaccine into the childhood vaccination programs in this region. METHODS: Data on cervical cancer, cervical screening programs, childhood immunization and HPV vaccination programs for Nordic countries were searched via PubMed and various organizations. We furthermore contacted selected experts for information. RESULTS: The incidence of cervical cancer is highest in Greenland (25 per 100,000, age standardized, World Standard Population, ASW) and lowest in Finland (4 per 100,000 ASW) and rates in the other Nordic countries vary between 7 and 11 per 100,000 ASW. Greenland and Denmark were first to introduce HPV vaccination, followed by Norway. Vaccination programs are underway in Sweden and Iceland, while Finland has just recently recommended introduction of vaccination. HPV vaccination has been intensively debated, in particular in Denmark and Norway. DISCUSSION: In Nordic countries with a moderate risk of cervical

cancer and a publicly paid health care system, the introduction of HPV vaccination was a priority issue. Many players became active, from the general public to health professionals, special interest groups, and the vaccine manufacturers. These seemed to prioritize different health care needs and weighed differently the uncertainty about the long-term effects of the vaccine. CONCLUSION: HPV vaccination posed a pressure on public health authorities to consider the evidence for and against it, and on politicians to weigh the wish for cervical cancer protection against other pertinent health issues.

Sander BB, Vazquez-Prada M, Rebolj M, Valentiner-Branth P, Lynge E**.** (2015) "Mothers' and their daughters' use of preventive measures against cervical cancer." Scand J Public Health **43**(4):415-22.

Widgren K, Simonsen J, Valentiner-Branth P, Molbak K. (2011). "Uptake of the human papillomavirus-vaccination within the free-of-charge childhood vaccination programme in Denmark." Vaccine **29**(52):9663-7.

Casadevante V, Cantarero-Arévalo K, Cuesta JG, Valentiner-Branth P. (2016). "Ethnic background and Human Papillomavirus vaccine uptake in Denmark: a countrywide retrospective cohort study including 274,154 women aged 19-28 years**."** Papillomavirus Research **2**: 78–84.

AIM: We examined ethnicity-related differences in the uptake of a temporary free-of-charge HPV vaccine (HPVV) catch-up programme offered in Denmark from August 2012 to December 2013 to women born from 1985–1992 and compared it with the previous self-payment system in place. METHODS: We conducted a nationwide retrospective cohort study. We performed logistic regression analyses to examine the relationship between ethnic background and HPV vaccine (HPVV) programme initiation. RESULTS: The free programme increased the vaccination uptake from 16% to 75%. Descendants (Denmark-born women with both parents of foreign origin) and immigrants in Denmark for more than 5 years were less likely to initiate the free HPVV programme than Denmark-born women ((aOR=0.56; 95% CI: 0.54–0.59) and (aOR=0.39; 95% CI: 0.38–0.40), respectively). The likelihood of HPVV programme initiation among immigrants increased with time in Denmark ((aOR=2.28; 95% CI: 2.11–2.48) for immigrants living in Denmark for 16–20 years compared to 6–10 years)). CONLUSION: The initiation of the free-of-charge HPVV programme was satisfactory. However, large differences in uptake were demonstrated, indicating that some target groups are harder to reach than others. The integration process (as related to use of health services) occurs over many years where differences between the different population groups seem to vanish.

Mølbak K, Hansen ND, Valentiner-Branth P. (2016). "Pre-Vaccination Care-Seeking in Females Reporting Severe Adverse Reactions to HPV Vaccine. A Registry Based Case-Control Study." PLoS One **11**(9):e0162520.