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Natural history and biological behaviour of human papillomavirus: implications for cervical cancer screening

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One of the cancers where the causative link between viral infection and carcinogenesis is very strong is cervical cancer. Virtually every cervical carcinoma harbours human papillomavirus (HPV) genome. Whether an HPV virus such as HPV 16 induces an invasive cancer is not solely determined by the characteristics of the virus itself but also by genetic factors of the host. HPV infections are principally sexually transmitted and cause various diseases in the anogenital region. The prevalence of HPV infections ranges between 20% and 80% in sexually active adults. The majority of HPV infections remain asymptomatic. Their evolution is variable, leading either to growth, persistence or spontaneous regression. Infected patients may develop lesions of different extent: low-grade preneoplastic lesions (CIN I), high grade precancerous stage (CIN II-CIN III), carcinoma *in situ*, and ultimately invasive cervical carcinoma. It is still questionable whether HPV detection can be used as a primary screening tool instead of classical cervical cytology or as merely an adjunct to cervical cytology. HPV testing may have a role as a complementary test to identify concealed high-grade lesions among women with repeated low-grade or inconclusive cytological smears. HPV is a transient infection in most women, especially in the age group of 15–35 years, the majority of infections being cleared spontaneously. Therefore HPV detection is not useful as a primary screening tool in women younger than 35 years. In older women this method could be useful, but it should be further evaluated in clinical trials.

Key words: human papillomavirus, cervical cancer, CIN, screening

INTRODUCTION

Viruses and human cancer

Cancer is a disease of uncontrolled cell growth, where a cell with mutated DNA stops following the normal instructions that govern its life as part of the body. Carcinogenesis is a process by which agents that can cause mutations in the cellular DNA lead to cancer. There are basically three groups of carcinogens: viruses, physical agents such as radiation, and chemical agents.

A prime example of viral carcinogenesis is adult T-cell leukemia secondary to infection with the retrovirus HTLV-1. HTLV-1 infection predominantly involves CD4 T-helper lymphocytes. An HTLV-1 protein tax causes an increase in the number of interleukin 2 (IL-2) receptors on infected lymphocytes leading to a polyclonal lymphocytosis as a first step to develop a lymphoid malignancy.

Another malignant tumour is pleural mesothelioma, where the effects of chemical carcinogen asbestos interact with the polyomavirus SV40 to induce pleural neoplasia in genetically susceptible individuals. Small t-antigen and large T-antigen are the viral proteins that not only play a role in the viral life cycle, but also exert oncogenic effects (1, 2). They interact with host proteins such as inactivation of the p53 protein by binding this protein and by influencing the telomeres resulting in an enhanced lifespan of a given cell clone (3). Similar mechanisms have been described by infection with other viruses such as EBV virus (lymphoproliferative diseases in the immunocompromised host), hepatitis B and hepatitis C leading to the development of hepatocellular carcinoma and human herpes 8 (HHV-8) giving rise to Kaposi sarcoma.

One of the cancers where the causative link between viral infection and carcinogenesis is very strong is cervical cancer. Virtually every cervical carcinoma

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harbours the human papillomavirus (HPV) genome. The gene products of the early genes E6 and E7 are known to bind and inactivate by this way the gene products of the suppressor genes retinoblastoma (Rb) and p53. The HPV virus exists intracellularly in its episomal form in the early stages of the infection but can integrate in the genome of the host thereby taking control and even enhancing the transcription over several host genes including oncogenes and genes regulating the telomeres. This results in cell clones with an enhanced growth rate leading to the development of a malignant cell population. Whether an HPV virus such as HPV 16 induces an invasive cancer is not solely determined by the characteristics of the virus itself but also by the genetic factors of the host. Certain single nucleotide polymorphisms (SNP) in the genome of the host itself seem to carry an enhanced risk for this individual to develop an invasive cervical carcinoma, especially the polymorphism at the codon 72 of the p53 gene. The arg/arg phenotype seems to carry a higher risk than the pro/pro phenotype and the heterozygous pro/arg phenotype (4).

Human papillomavirus infections are among the most common chronic viral infections in humans and are considered to be the major causative agent of cervical carcinoma (5). They are principally sexually transmitted and cause various diseases in the anogenital region. The prevalence of HPV infections ranges between 20% and 80% in sexually active adults, depending on the various risk factors. The majority remains asymptomatic (6). It is estimated that 1 million new cases of HPV disease are diagnosed annually in the U.S.A., and approximately 500,000 new cases of cervical carcinoma develop annually worldwide (7). Over 95% of these tumours contain DNA from high risk HPV types (8). To date, more than 80 types of papillomaviruses have been identified, and others are still being characterized. These viruses can be differentiated as they are both species and tissue specific, and some are benign and others lead to the development of cancer. In humans, HPV can be therefore subdivided into *low-risk* and *high-risk* HPV, which are associated with the development of cancers, mainly in the genital area, and also according to the site of the infection, *i.e.* either cutaneous or mucosal.

Transmission of HPV viruses

Transmission occurs usually through sexual contact. HPV is resistant to heat and desiccation and is therefore very stable. Up to 60% of individuals will develop disease after a single sexual contact with an infected partner: the number of sexual partners appears to be the most important risk factor for the acquisition of HPV (9). The virus is thought to penetrate trough microlesions in the skin or mucous membranes: semen probably plays a major role in transmission, and prostate could be an important reservoir. There is a variable interval between the exposure and the development of HPV lesions, ranging from 8 weeks to 8 months.

Vertical transmission from infected mothers to neonates probably occurs very frequently, but rarely leads to development of disease. If it does occur, the infection may persist for many years in the mouths of these children (10). Neonatal infection, with HPV 6 or more frequently HPV 11, may lead to the development of laryngeal papillomatosis in a small percentage of babies. High risk HPV types may be detected in the mouths of babies for several months or even years after delivery.

Transmission could also occur without physical contact owing to high stability of the virus. Transmission has been described through contaminated fomites, infected towels or clothes, surgical instruments, babies bathing with an infected mother, and its presence has been detected even in the plume generated by laser evaporation of warts (11).

Molecular biology of human papillomavirus

The human papillomavirus (HPV) contains circular, double-stranded DNA, 7900 bp in length, contained within a capsid. There is no outer envelope, which makes the virus somewhat labile in the environment. There are at least 70 strains of HPV with a different disease causing potential.

The viral genome consists of a control region, which contains regulatory genes. These regulatory genes help the virus use some of the infected cell's machinery for replication of the virus. One of these genes is a promotor gene sensitive to the cell's RNA polymerase. The machinery within the cell for transcribing and translating DNA to RNA to protein can be used by the virus for replication. This is a common mechanism in viruses that replicate within a host cell. The virus can have a much smaller genome, since it "borrows" gene functions from the cell. Downstream from the control region is a long open reading frame (ORF), which encodes genes controlling viral growth as well as the viral structural proteins. These genes are divided into early (E) and late (L). The genome is divided into two regions: the early region, which usually contains seven (E1, E2, E3, E4, E5, E6 and E7) coding for viral replication and transformation, and the late region containing two open reading frames (L1 and L2) (12). These L1 and L2 genes encode proteins for the viral capsid. Viral amplification occurs via E1 helicase and E2 transactivator (13).

Two of the HPV genes, E6 and E7, are of special interest. These genes have a transforming or oncogenic potential for human cells. The E6 and E7 proteins can inactivate the proteins from the human tumour suppressor genes p53 and Rb protein. When p53 protein is inhibited by interference from the E6 protein, the infected epithelial cell can enter S-phase of the cell cycle without being checked. With p53 inhibited by HPV, the cell's entrance into S phase is deregulated, greatly increasing the possibility that errors in DNA synthesis will occur with subsequent mutations. The E7 protein has a similar interaction with the Rb protein. Again, this interaction leads not only to inhibition of another suppressor gene product but also to the potential for more mutations as the unchecked aqueous epithelial cells proliferate.

The E6 and E7 proteins are continuously expressed within tumour cells and are necessary to maintain the transformed state (14).

Infection of the cervix usually occurs at the squamocolumnar junction of the ecto-endocervix, or the transformation zone. Limited replication occurs in the suprabasal layers of the epithelium, with expression of early ORF proteins. As infected cells mature and move upwards to the more superficial layers of the epithelium, the late proteins L1 and L2 are expressed to form capsids. Viral shedding does not occur within the epithelium and mature viruses are only shed externally (12). In the case of oncogenic viruses, E6 and E7 proteins transform the cells leading to carcinoma *in situ* and invasive carcinoma. Benign tumour cells contain episomal DNA and capsid proteins, whereas CIN lesions and cancer also contain HPV DNA integrated into host DNA. Once integrated, HPV 16 DNA is non-replicating and non-infectious. E6 and E7 proteins are expressed at high levels in cervical cancer.

Time course of cervical carcinogenesis

Many factors are thought to induce dysplasia. Infection with HPV is by far the most common. Dysplasia develops in a high percentage of individuals with HPV detected on the cervix. Some patients with dysplasia will revert and return to normal, while others will progress to high-grade lesions and even invasive cancer.

About 15% of women will at some time in their life have detectable HPV on a cervical swab, with the incidence peaking between 15 and 30 years. Dysplasia usually detected as LSIL or HSIL on cervical cytology occurs in as many as 90% of HPV-infected individuals with a peak incidence between 25 and 45 years. Invasive carcinoma of the cervix should be a rare disease. Its incidence is a reflection of the effectiveness of screening programs. The incidence is low in women who have regular cervical cytology. Severe or moderate dysplasia is treated in these patients before progression to carcinoma can occur. Cancer has its peak incidence between 45 and 65 years of age (15).

Life cycle of HPV infection

The HPV viral life cycle includes three phases: immediate cell lysis with release of the virus, latent viral infection, and integration of HPV DNA into cellular DNA.

Exposure of squamous epithelial cells to HPV results in infection of a certain percentage of basal cells. HPV-infected basal cells can follow several different courses. In an active or productive infection, propagation of virus inside the cell leads to cell lysis and release of free infectious viral particles. The virus may also enter a latent phase, not replicating or doing anything, just staying around in the cell cytoplasm. These cells will likely mature becoming an anucleate shed squamous cells thereby clearing the virus from the epithelium. Latent infection can also activate at some time in the future (14).

The third possibility is integration of the viral genome into the host genome. This step is crucial for inducing the start of viral-induced carcinogenesis. The suppression or inactivation of the gene products of the suppressor genes, *e.g.*, p53 and/or Rb by the E6 and E7 proteins of the virus, as well as induction of mutations in the host genome can trigger a clonal expansion. Squamous cell dysplasia (LSIL and HSIL) is a clonal neoplastic process as shown by the fact that each single virus enters the host DNA at a slightly different location. Multiple dysplastic clones coexist, indicating that initiation of neoplasia following viral integration is common. These clones over a span of time of approximately nine years lead to invasive squamous cell carcinoma.

We do not know exactly which factors favor integration of viral DNA into the cell's genome. Possibly one of the more important factors is the HPV type and then especially HPV 16, which seems to bear a higher risk for integration. The high risk strains not only show a higher binding of E6 and E7 proteins to tumour suppressor genes, also but seem to integrate much easily in the host genome. Viral load and host specific factors such as genetic susceptibility and local immunity seem also to play an important role.

High risk and low risk HPV types

To date, more than 80 HPV subtypes have been identified and others are still being characterized.

These viruses can be differentiated as they are both species- and tissue- specific. In humans, some HPV types lead to cancer, therefore they are designated as *high-risk* types, while others rarely or never lead to malignancy and are considered as *low-risk* types. HPV types 16, 18, 31, 33, 39, 45, 52, 56, 58, 59, 66, 68 are regarded as *high-risk* types as they may cause squamous cell carcinoma and premalignant cervical lesions.

HPV 6 and HPV 11 are the most frequent *low-risk* HPV types found in humans and are mainly responsible for the development of genital warts. HPV 6 is mostly found in immunocompetent people, whereas HPV 11 is frequently found in immunosuppressed people (16). These benign tumours develop on the internal and external anogenitalias and are presented either as cauliflower- like warts designated as *condylomata accuminata*. When the infection develops, internally it is most common in the form of flat warts. Their evolution is variable, leading either to growth, persistence or spontaneous regression. The mean regression rate is 2–11% in 3 months. The incidence of infection with a low-risk HPV type is estimated to be 12.4 cases/1000 women/month. The mean duration of persistent infection with a low-risk HPV type such as HPV 6 is less than 10 months (22).

Infection with high-risk HPV can evolve to lowgrade preneoplastic lesions (CIN I), to high-grade precancerous stage (CIN II-CIN III), to carcinoma *in situ*, and ultimately to invasive cervical carcinoma (7). The incidence of infection with a high-risk HPV type is estimated to be 14.0 cases/1000 women/month. The mean duration of persistent infection with a high-risk HPV type such as HPV 16 is 18.3 months with a clearance of 12% every two years.

Only a small percentage will progress from one step to the next, and this process usually takes several years. On the other hand, Critchlow and Kiviat support the hypothesis that some high risk HPV infections are CIN III from the onset (17). Persistent infection with a high-risk HPV is a prerequisite for the development and maintenance of CIN III. A high viral load has been associated with persistent HPV infection and increased risk for the development of dysplasia and ultimately carcinoma.

Cytological progression of cervical cancer

Squamous cell carcinoma of the uterine cervix takes years, even decades to progress from the earliest histological abnormality of low-grade dysplasia to invasive cancer. In fact, it is an illustration of the multistep evolution over years. There are many gaps in our knowledge about cervical cancer. Cervical cytology has been our principal tool for observing the cervix and detecting cervical carcinoma and/or its precursor lesions. Within the cervical canal, the epithelium of the cervix makes an abrupt transition from squamous to columnar. Inflammation and hormonal influences alter this rather sharply defined transition zone. Cells shed from this zone are preferentially investigated by cervical cytology.

About 15% of women demonstrate some abnormality in maturation of the squamous epithelium as seen with cervical cytology. The terminology to describe these morphological aberrations is defined in the Bethesda classification for reporting on cervical cytology samples.

The minimal disruption of cytology is called ASCUS (atypical squamous cells of undetermined significance). Approximately one third of the cytology specimens reported as ASCUS harbour HPV DNA. The women who demonstrate this cytological picture of ASCUS/HPV generally go onto LSIL (low grade squamous intraepithelial lesion). The mean time for progression from ASCUS to LSIL is about 4 years, but is also dependent on whether an HPV of low-risk or high-risk type is involved (67 months versus 88 months). Patients with LSIL usually revert to ASCUS and further to normal without treatment, with a mean regression time 7.8 months for low-risk HPV types and 13.8 months for patients infected with a high-risk HPV type towards ASCUS and further to normal with a mean regression time 7.7 months for low-risk HPV types and 16.8 months for patients infected with a high risk HPV type, particularly in the group of women aged 19 to 35, where approximately 90% revert to normal. Only 10 to 20% of LSIL cases continue to the next stage, HSIL (high grade squamous intraepithelial lesion). This progression also takes approximately 4 years and is estimated to be 3–5% of the cases/year with a mean progression time of 83.5 months for so-called low-risk HPV types and 73.3 months for high-risk HPV types (22). A long-term follow-up study in the Netherlands revealed that women with abnormal cytology and high-risk HPV-infection were 29 times more at risk of developing CIN III than HPV negative women (18). HSIL is also called severe dysplasia or carcinoma *in situ*. Whether HSIL is reversible remains an open question. However, some studies suggest that a small percentage of HSIL cases may regress spontaneously to lower grade lesions with a mean regression time 8.9 months for low-risk HPV types and 17.1 months for patients infected with a high-risk HPV type. The classical treatment of HSIL is an excisional cone biopsy resulting in cure at this stage. When no treatment is given, the majority of HSIL will progress to micro-invasive and widely invasive squamous cell carcinoma.

Dysplasia is a descriptive histological term including both LSIL and HSIL. Histology shows an epithelium where the basal squamous cells fail to mature as they age and migrate upwards to the more superficial layers.

Techniques for human papillomavirus testing

Most basic and clinical investigations use one or more of three nucleic acid -based tests to detect and type HPV (19). These tests include a hybrid capture system, *in situ* hybridization, and polymerase chain reaction (PCR). Presently the hybrid capture I and II assays show good reliability and accuracy. Hybrid capture II is a commercial HPV detection test designed to detect 18 HPV types, divided into the high-risk and low-risk groups. The sensitivity of the HC II was compared with cytology in detecting HSIL by comparing the results with biopsy outcomes and was found to be 85.3%, *i.e.* higher than conventional cytology (19).

For evaluation of different HPV subtypes, *in situ* hybridization is equivalent to PCR but less sensitive although less cumbersome. The pattern of *in situ* hybridization can give information whether the HPV virus is still present in the episomal form or is already integrated into the host genome. A speckled nuclear staining pattern for HPV DNA is considered to be suggestive of the episomal form where a diffuse nuclear staining would be indicative of HPV DNA integration into the host genome, the latter being necessary for oncogenesis (20).

PCR primers are so sensitive that they can distinguish among tiny regional base pair changes. The PCR methodology may be used in the future to study variants of the same HPV subtype such as HPV 16 to understand why only a fraction of these high risk HPV infections evolve into invasive cancer.

There is a new RNA based NASBA type detection system (www.norchip.com) that detects HPV RNA of high risk types 16, 18, 31, 33, 35, 39 and 45 claiming that the detection of E6/E7 RNA is significant more informative, as this is related to a metabolically active oncogenic HPV virus where DNA testing gives information only on the presence or absence of the virus. The criticism is the following: an inactive virus will not be detected by RNA screening and it can get active afterwards: false negative screening by RNA based methodology. It is better to combine both methodologies: first screen on the DNA level, and if you find a virus check then whether it is transcriptionally active or not. Another point is that NORCHIP does not detect all high-risk types. It is too early to decide for or against this methodology.

Indications for detecting HPV

Patients with normal cytology

It is still questionable whether HPV detection can be used as a primary screening tool instead of classical cervical cytology or merely as an adjunct to cervical cytology, especially in the group of women aged 15 to 34 years. ***We think there is no place for HPV DNA detection as a screening tool.*** This is very well illustrated in the study of Woodman and coworkers. They investigated 1075 women in the age group 15–39 years with cervical cytology every six months and HPV DNA testing with a follow-up period of five years. They found a cumulative risk of 44% for acquiring one or more HPV infections, with an average rate of 21% of women with HPV infection. HPV 16 was the most common type. They found that HPV DNA positivity preceded cytological aberrations with in 6 months. Different infections were noted with different HPV types in the same patients during the follow-up period which lasted approximately 5 years. The cumulative risk at three years of detecting another high-risk HPV type not present in the first positive sample was 26%. More than 90% of HPV infections regressed with a mean duration from 6 months to 2 years. HPV 16 and HPV 18 were found to be the most prevalent, the former persisting longer (21).

In pregnancy, HPV reactivation is frequently seen due to the decreased immunity. Lesions can evolve rapidly and even progress to HSIL. However, regression is seen in most cases after delivery even high-grade lesions. Only in cases of cervical carcinoma elapsing during pregnancy the therapeutic action can be considered.

Patients with abnormal cytology

ASCUS

This can be considered as one of the major indications for detecting possible HPV DNA. In approximately one third of the ASCUS cases HPV DNA is present with a preponderance of high risk HPV types (75%), especially HPV 16. Behind HPV-positive ASCUS cytology you find roughly 60% of SIL lesions, 16–45% of HSIL lesions and 38% of LSIL. In 2% of the cases that are ASCUS HPV DNA-positive, an invasive cervical carcinoma is found. ***This means that ASCUS HPV-positive patients have to undergo colposcopy with eventual biopsy***. Another possibility is that the patient is re-evaluated after 4 to 6 months by cytology and HPV testing. When both investigations are negative, the patient returns to the normal routine screening scheme. Patients with per-

sisting aberrant ASCUS cytology and/or HPV DNA positivity are referred for colposcopy. The chance of finding a HSIL lesion after ASCUS cytology with HPV DNA negativity is only 5%.

Patients with ASC-H (ASCUS cannot exclude HSIL) are directly referred for colposcopy and when negative can be retested with cytology and /or HPV DNA testing after 6 months (22, 23).

Low- and high-grade lesions (*LSIL and HSIL*)

Virtually all LSIL (97.5%) and HSIL lesions (100%) contain HPV DNA with a preponderance of high risk HPV types. Detection of HPV DNA can be used as a quality control in the cases morphologically diagnosed as LSIL or HSIL. Several studies suggest that triage by high-risk HPV subtype in the setting of low-grade cytological change has a good sensitivity and specificity. However, there are still conflicting data. ***Patients with LSIL in the presence of a high-risk HPV seem to be at a higher risk of progression to HSIL as well as a high viral load. Determination of the exact HPV type can be used in the follow-up of SIL lesions, both low-grade and high-grade.***

The discriminative capacity of HPV DNA testing was evaluated in 43 patients with abnormal cytology, who had previously undergone treatment for cervical dysplasia. The HPV test was positive in all patients with recurrence of dysplasia with a sensitivity and specificity of 100% and 44%, respectively. Overall, although HPV testing has been found to be complementary for the diagnosis of cervical dysplasia, it has a limited value in a well-screened population. HPV testing may have a role as a complementary test to identify concealed high-grade lesions among women with repeated low-grade or inconclusive cytological smears. HPV testing can be useful in the follow-up of surgery after dysplasia (conization) or carcinoma (hysterectomy). The negativity for HPV DNA is indicative of a complete regression of the disease, although one must take into account that HPV is cleared after 10 to 12 months after surgery in 63.5% to 94% of patients. Factors influencing the rate of the viral clearance after surgery include age, lesion grade (CIN II, CIN III), complete removal of the lesion and the volume of the cone in cases of dysplasia lesion (21, 23).

CONCLUSIONS

HPV is a transient infection in most women, especially in the age group 15–35 years, the majority of infections being cleared spontaneously.

Therefore HPV detection is not useful as a primary screening tool in women younger than 35 years. In older women this method could be useful, but it should be further evaluated in clinical trials. At this moment, the triage of ASCUS is one of the key indications for HPV detection and subtyping. Detection of the HPV virus and subsequent subtyping can be useful as a quality control for both LSIL and HSIL and may also bear a prognostic significance. Another useful application is the post-surgery follow-up of conizations (SIL lesions) and cervical carcinoma patients.

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ŽMOGAUS PAPILOMOS VIRUSO BIOLOGINĖS FUNKCIJOS IR INFEKCIJOS VYSTYMASIS: JO REIKŠMĖ GIMDOS KAKLELIO PATOLOGIJOS PATIKROS PROGRAMOSE

S a n t r a u k a

Gimdos kaklelio vėžio vystymasis yra glaudžiai siejamas su virusine infekcija. Beveik visuose gimdos kaklelio navikuose randama žmogaus papilomos viruso (ŽPV) DNR. Tačiau piktybiniame procese svarbus ne tik ŽPV, ar ypač ŽPV 16 tipas, bet ir paties šeimininko genetiniai veiksniai. ŽPV virusai dažniausiai plinta lytinio kontakto metu sukeldami įvairius anogenitalinės srities susirgimus. Tarp lytiškai aktyvių asmenų infekuotumas ŽPV svyruoja nuo 20 iki 80%. Infekcija gali progresuoti, išsilaikyti ar spontaniškai išnykti. Daugelis šių infekcijų nepalieka jokių klinikinių pasekmių. Didelės vėžio rizikos ŽPV gali lemti neryškią, vidutinę ir ryškią gimdos kaklelio displaziją (CIN I, CIN II, CIN III), neinvazinio vėžio (*carcinoma in situ*) bei invazinio gimdos kaklelio vėžio vystymąsi. Vis dar diskutuojama dėl ŽPV tyrimo įtraukimo į gimdos kaklelio patologijos patikros programas: ar šis tyrimas turėtų pakeisti klasikinį citologinį tyrimą, ar jį papildyti. ŽPV nustatymas gali padėti atskleisti neišryškėjusius didelio laipsnio intraepitelinius pokyčius moterims, kurioms, atlikus pakartotinus citologinius tepinėlius, rasta nedidelių pakitimų ar citologinio tepinėlio išvada neaiški. ŽPV yra dažniausiai savaime praeinanti infekcija 15–35 metų moterims. Taigi dėl šios infekcijos netikslinga tirti moteris iki 35 metų. Vyresnėms moterims šis tyrimas galėtų būti taikomas, tačiau galutinė jo reikšmė bus įrodyta ateityje, atlikus klinikines studijas.

Raktažodžiai: žmogaus papilomos virusas, gimdos kaklelio vėžys, CIN, patikra