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## Breast cancer epidemiology

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**Key words:** Breast Neoplasms; Epidemiology; Incidence; Mortality  
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Breast cancer is the most common cancer among women worldwide, accounting for more than one million (23%) of all newly diagnosed cancers and about half a million (15%) of cancer's deaths.

There are substantial variations in breast cancer rates among different countries. Those are some six times higher in the U.S., Canada or Northern Europe than in Asia or Africa. There has been a sustained increase in the incidence of breast cancer in developing countries in recent years. In some regions like North America, Western Europe and Australia, breast cancer mortality has started to decrease, mainly due to improvements in early detection (mammography screening programs) and treatment. Five-year relative survival rates are higher than 70% in most developed countries.

In Province of Vojvodina, based on official data from Cancer Registry of Vojvodina – Oncology Institute of Vojvodina, breast cancer in women has been ranking first in both incidence and mortality, for many years. In 2005, 973 women were newly diagnosed with breast cancer (26%) and 562 had died (22%). The age-standardized incidence rate in 2005 (standardized to the World Standard Population) was 56.75 per 100,000 women and the lifetime risk (to 75 years) of those being diagnosed with breast cancer was about one in 16. Breast cancer incidence rate in Vojvodina ranks at low level in the European scenario, similarly to the situation in Central Serbia, Slovenia, Croatia and Czech Republic. The age-specific incidence and mortality rates are increasing by the age with the peak in age group of 60-64 for incidence (221/100,000) and 80-85 for mortality (182/100,000). The age-standardized mortality rate in 2005 was 30 per 100,000 women.

Both incidence and mortality have been increasing throughout the period 1978-2004 significantly. The annual percent change over that period was +1.03%.

Diagnosis of early breast cancer in Vojvodina by organized mammographic screening activity, concerning improvement of epidemiological situation, should be introduced.

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## Risk factors for breast cancer

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**Key words:** Breast Neoplasms; Risk Factors

Risk factors for breast cancer are:

### Age

The incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. Compared with lung cancer, the incidence of breast cancer is higher at younger ages. In some countries there is a flattening of the age incidence curve after the menopause.

### Age at menarche and menopause

Women who start menstruating early in life or who have a late menopause have an increased risk of developing breast cancer. Women who have a natural menopause after the age of 55 are twice as likely to develop breast cancer as women who experience the menopause before the age of 45. At one extreme, women who undergo bilateral oophorectomy before the age of 35 have only 40% of the risk of breast cancer of women who have a natural menopause.

### Age at first pregnancy

Nulliparity and first birth at late age both increase the lifetime incidence of breast cancer. The risk of breast cancer in women who have their first child after the age of 30 is about twice that of women who have their first child before the age of 20. The highest risk groups are those who have a first child after the age of 35; these women appear to be at even higher risk than nulliparous women. A birth of a second child at early age further reduces the risk of breast cancer.

### Family history

Up to 10% of breast cancer in Western countries is due to genetic predisposition. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance. This means that it can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves. It is not yet known how many breast cancer genes there may be. Two breast cancer genes, BRCA1 and BRCA2, which are located on the long arms of chromosomes 17 and 13 respectively, have been identified and account for a substantial proportion of very high risk families—i.e. those with four or more breast cancers among close relatives. Both genes are very large and mutations can occur at almost any position, so that molecular screening to detect mutation for the first time in an affected individual or family is technically demanding. Certain mutations occur at high frequency in defined populations. For instance, some 2% of Ashkenazi Jewish women carry either BRCA1 185 del AG.

### Familial breast cancer — criteria for identifying women at substantial increased risk

- One first degree relative with bilateral breast cancer or breast and ovarian cancer **or**
- One first degree relative with breast cancer diagnosed under the age of 40 years or one first degree male relative with breast cancer diagnosed at any age **or**
- Two first or second degree relatives with breast cancer diagnosed under the age of 60 years or ovarian cancer at any age on the same side of the family **or**
- Three first or second relatives with breast and ovarian cancer on the same side of the family.

The first degree relative is a mother, a sister or a daughter. The second degree female relative is a grandmother, a granddaughter, an aunt or a niece.

### Criteria for identifying women at very high risk in whom the gene testing might be appropriate

Families with four or more relatives affected with either breast or ovarian cancer in three generations and one alive, affected relative.

### Previous benign breast disease

Women with severe atypical epithelial hyperplasia have (4 – 5 times) higher risk of developing breast cancer. Women with palpable cysts, complex fibroadenomas, duct papillomas, sclerosis adenosis, and moderate or florid epithelial hyperplasia have a slightly higher risk of breast cancer (1.5 – 3 times).

### Radiation

Ionising radiation also increases risk later in life, particularly when exposure is during rapid breast formation. Mammographic screening is associated with a net decrease in mortality from breast cancer among women aged over 50.

### Lifestyle

**Diet:** Although there is a close correlation between the incidence of breast cancer and dietary fat intake in populations, the true relation between fat intake and breast cancer does not appear to be particularly strong or consistent.



**Weight:** Obesity is associated with a twofold increase in the risk of breast cancer in postmenopausal women whereas among premenopausal women it is associated with a reduced incidence.

**Alcohol intake:** Some studies have shown a link between alcohol consumption and incidence of breast cancer, but the relation is inconsistent and the association may be with other dietary factors rather than alcohol.

#### Oral contraceptive

While women are taking oral contraceptives and for 10 years after stopping these agents, there is a small increase in the relative risk of developing breast cancer. There is no significantly increased risk of having breast cancer diagnosed 10 or more years following cessation of the oral contraceptive agent. Cancers diagnosed in women taking the oral contraceptive are less likely to be advanced clinically than those diagnosed in women who have never used these agents, relative risk 0.88 (0.810.95). Duration of use, age at first use, dose and type of hormone within the contraceptives appear to have no significant effect on breast cancer risk.

#### Hormone replacement therapy

Among current users of HRT and those who have ceased the use 1 – 4 years ago, the relative risk of having breast cancer diagnosed increases by a factor of 1.023 (1.0111.036) for each year of use. This increase is consistent with the effect of a delay in the menopause, because the relative risk of breast cancer increases in never users by a factor of 1.028 (1.0211.034) for each year older at the menopause. The risk of breast cancer appears higher with combined oestrogen and progestogen combinations.

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## Hereditary breast and/or ovarian cancer in Serbia: Our experience in genetic testing and counseling

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**Key words:** Breast Neoplasms; Ovarian Neoplasms; Genetics; Genes, BRCA1; Genes, BRCA2; Mutation; Neoplastic Syndromes, Hereditary

Breast cancer is the most common female cancer worldwide, as well as in Serbia. The incidence of breast cancer increases in Serbia - it can be described with about 4000 newly diagnosed cases per year. (1). Up to 10% of all breast cancer cases are present with a striking family history, suggestive of Mendelian inheritance, mostly associated with loss-of-function of strongly penetrant germline mutations in BRCA1/2 genes. Probability that mutation will be found in the family rises if family history includes cancer cases with early ages of onset, especially for BRCA1 mutation. Even among multi cases families (4 or more cases), BRCA1 or BRCA2 mutations were found in only 65% of cases (2). Furthermore, new data underline that the prevalence of BRCA1/BRCA2 mutations in hereditary cancer cases may be overestimated (3). The BRCA genes penetrance that influences life-time risk of developing breast and/or ovarian cancer is still intensively investigated. BRCA1/BRCA2 mutation significantly elevates lifetime risk for the development of breast cancer -about 5 to 8 fold for BRCA1 and 4 to 7 fold for BRCA2 in comparison with breast cancer risk in general population of about 10%. Ovarian cancer life-time risk associated with BRCA1 harmful mutation is about 40%, while BRCA2 mutation carriers harbor lower life-time risk of 20% (2). Besides by BRCA1 and BRCA2 harmful mutations, elevated risk for breast cancer in certain rare syndromes is caused by mutations in other genes such as p53 (Li-Fraumeni), PTEN (Cowden), STK11 (Peutz-Jeghers) etc. It seems that, besides mutations in high penetrance genes BRCA1 and BRCA2, alterations of intermediate or low penetrance genes that are more frequent in population, possibly account for a significant proportion of unexplained familial clustering of breast cancer. Concerning their cell function, it can be noticed that most of the genes whose mutations influence elevated breast cancer risk are involved in DNA signaling and repair - both main genes in hereditary predisposition to breast cancer, BRCA1 and BRCA2 are key players in DNA repair by homologous recombination (4). Nevertheless, hereditary breast and ovarian cancer, associated with pathogenic BRCA1 and BRCA2 mutations, is the most frequent hereditary cancer syndrome which underlies the importance of genetic testing in potential BRCA mutation carriers. BRCA testing is not screening test for general population, due to the small proportion of hereditary form of disease, as well as to the high cost of testing. It is addressed to selected part of population that fit to recommended criteria. Full coding region sequencing of both genes is "gold standard" for detection of BRCA mutation(5). In parallel with developing detection methods, prevention strategies, including clinical, surgical and medical interventions became available in order to reduce cancer risk (6). Growing knowledge indicates limitations in genetic testing from the aspect of BRCA gene penetrance, unclassified BRCA variants and negative result interpretation. BRCA mutation carriers are faced with difficult choice regarding their health due to the fact that invasive prevention strategies such as prophylactic surgery demonstrate better results in risk reduction than regimens including self and clinical-examination. About 1400 breast cancer cases (about 35% of newly diagnosed cases in Serbia) are annually newly diagnosed at the Institute of Oncology and Radiology of Serbia and that is why we introduce genetic testing for hereditary breast/ovarian cancer in clinical practice. We formed blood bank with about 300 samples from families at risk for hereditary form of disease. So far, complete or partial analysis of BRCA 1/2 coding regions has been performed for 87 probands from 73 families. The observed mutation frequency was 12.6%. Identification of BRCA mutations carriers, establishment of spectra and frequency of BRCA mutations carriers, especially for those with developed breast cancer, together with long-term follow-up of mutations carriers, should allow the research on the factors affecting BRCA genes penetrability. Systemic BRCA analysis will enable introduction of clinical management for mutation carriers into the clinical practice of Serbia, resulting with the real benefit for this highly vulnerable part of population.

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## What should be the histological gold standard?

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### Breast MRI and stereotaxic

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**Key words:** Breast Neoplasms; Diagnosis; Mammography; Magnetic Resonance Imaging

Breast cancer is the most common malignant neoplasm in female population. It is estimated that each ninth woman is affected during the lifetime. The incidence of the breast cancer has slightly increased during the last 50 years, in contrast to the majority of other malignancies in women, which show continuing decrease. In Vojvodina, around 800-900 new cases of breast cancer are discovered.

The complexity of early breast carcinoma diagnostics is conditioned by the variability of the breast structure during life, as well as cyclic, hormone conditioned changes.

Today, the most important and the most widely applied radiological modality is *mammography*, which value is proved by many studies. Nevertheless, the method also has its limits, the knowledge of which contributes to avoid falsely adverse results.

*Magnetic resonance* currently presents the most up-to-date visualization modality. Its basic technical possibilities, multiplanarity, high area and tissue resolution combined with biological non-invasiveness is unambiguously considered as the most sensitive and the most specific radiological method for evaluation of the majority of organism regions.

The protocol of breast screening includes the use of special surface coil, where the patient is in prone position. Examination technique is somehow different from the examination methodology of other body regions. Namely, contrast application is necessary while the dynamic study is mandatory, i.e. the monitoring of contrast dynamics within the respectively repeated time intervals.

The necessity of such a technique is based on the fact that both benign and malignant lesions result in postcontrast amplification of signal intensity, but in contrast to benign ones, malignant ones have the characteristic curve of the signal intensity increase. The biological basis of the contrast presentation in the malignant lesions is the consequence of the presence of neoangiogenesis, the phenomenon that is a typical form of invasive tumours; the presence of newly-created pathological capillary network is correlated with increased pathological vascularity, vascular permeability, as well as with the increase of interstitium in the malignant tumour (in comparison with the benign one) and the consecutive increase of the paramagnetic increase in the region of interest.

MR mammography is a highly selective examination that is performed within very narrow spectrum of indications when other available methods do not provide enough information.

*Absolute indications* for MR mammography are:

1. The evaluation of post-therapeutic breast with breast conserving surgical therapy (with or without radiotherapy) and evaluation of suspicious relapse in the zone of extensive scar.
2. The evaluation of silicon implant
3. The monitoring of neoadjuvant chemotherapy – MRM provides information about the reaction to therapy and the estimation of tumour viability.

*Relative indications* for magnetic resonant mammography are:

1. Dense breast, i.e. the breast with mammographically dense fibroglandular tissue that masks the potential malignity
2. In pre-surgery preparation in order to exclude multicentricities and bilateralism
3. Complicated findings where there is a discrepancy between clinical and radiological finding.
4. CUP (carcinoma unknown primary), i.e. with axillary metastatic illness potentially resulting from the breast, and with non-defined clinical/radiological finding.

It is important to emphasize that in particular cases MR mammography provides *no information*:

1. During pregnancy and lactation due to expressive hormonal stimulation and increased consecutive vascular permeability
2. Hormone substitutive therapy
3. Inflammatory process of malignant or non-malignant etiology
4. Detected microcalcifications

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## Imaging guided biopsies

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**Key words:** Breast Neoplasms; Biopsy, Fine-Needle; Biopsy, Needle; Ultrasonography, Mammary; Magnetic Resonance Imaging; Vacuum; Image Processing, Computer-Assisted

Breast cancer was diagnosed within the clinical setting until the 1970s when low-contrast mammography was introduced. Low-contrast mammograms were not highly efficient and gave way to ultrasound examination and, eventually, to modern mammography. Modern mammography allowed for the diagnosis of nonpalpable breast lesions and grading of DCIS with microcalcifications (1). Needle biopsy methods provided less invasive approaches to confirming whether a breast finding was benign or malignant.

### *Fine-needle Aspiration Biopsy*

Fine needle aspiration biopsy uses a small gauge needle to extract only a small amount of tissue and fluid from a suspicious area in the breast. Clear fluid suggests a benign finding, whereas bloody or cloudy fluid can indicate either a benign or a cancerous finding. In the past, stereotactic or ultrasound methods were used to guide the needle in cases where a mass could not be palpated. Today, most fine-needle aspiration biopsies are performed with ultrasound guidance. This is an outpatient procedure, and the patient receives a local anesthetic.

### *Core Needle Biopsy*

Core needle biopsy uses a slightly larger needle to withdraw small cores (cylinders) of tissue from an abnormal area. With this procedure, the needle is inserted into the breast several times (typically 3 to 6) to obtain adequate tissue samples (2). Although this also is an outpatient procedure, it is slightly more invasive than fine-needle aspiration biopsy because it involves a needle with a larger gauge (usually 9-14) and the removal of more tissue. However, results are more definitive than with fine-needle aspiration biopsy because more tissue samples can be examined (3). Typically, the needle is inserted by feeling for a mass, but a stereotactic method or ultrasound may be employed if a mass cannot be felt or is difficult to locate.

### *Stereotactic Core Needle Biopsy*

Stereotactic breast biopsy is indicated for women with **BI-RADS category 4** (suspicious) breast lesions (4). This is an outpatient procedure that typically uses ultrasound or, less often, mammography or MR imaging to guide the placement of the core needle into the area of the breast in which a mass or other suspicious finding is located. Using this method, a computer plots the coordinates of the mass and the needle is inserted into the precise location to extract the tissue sample.

### *Large-core Needle Biopsies*

Stereotactic methods or MR imaging are used to guide the needle for most large-core needle biopsies. One type of large-core needle biopsy is vacuum-assisted core biopsy. A hollow probe is inserted into the breast to suction a section of the suspicious tissue through an opening in the probe while a rotating knife within the probe cuts the sample from the surrounding breast tissue. More tissue samples can be obtained using a vacuum-assisted device than with standard core biopsy. Like standard core needle biopsies, large-core needle biopsies with vacuum assistance help physicians remove tissue using a single, small opening. The procedures are performed in outpatient settings and typically do not require suturing afterwards. Stereotactic breast biopsy uses radiological imaging to guide the biopsy needle. It involves inserting a biopsy device into the breast tissue to obtain a sample. Stereo comes from the Greek for "solid ordering." Ultrasound or, less frequently, mammography or MR imaging guides the placement of the percutaneous biopsy device. Computing combines with the imaging to determine the exact coordinates of a breast mass or other abnormal finding, allowing the physician to locate the area of interest with an accuracy of approximately 1 mm.

The upright, add-on unit used in stereotactic breast biopsy was introduced in 1988 to accommodate the automated needle biopsy gun (5). Large-core needle biopsy, guided by stereotactic techniques or ultrasound, was introduced in the 1990s (6). Stereotactic breast biopsy currently is performed using fine- to large-gauge needles with patients in either the upright or prone position.

Because the majority of suspicious lesions detected by mammography are benign, saving patients from unnecessary surgery is an advancement that improves patient care (7).

Stereotactic breast biopsy may be used when mammography indicates any of the following abnormal findings:

- A suspicious solid mass
- Microcalcifications
- Distorted breast tissue
- An area of abnormal breast tissue change
- A new mass or microcalcifications that have formed since a previous breast surgery



### Limitations

Stereotactic core breast biopsy may not be the most effective diagnostic method in all situations. When lesions are located near the chest wall, they may be hard to evaluate using stereotactic guidance. Patients with small breasts may require fine needle aspiration biopsy to prevent penetrating the chest wall with large-gauge or core needles (7). However, new biopsy devices allow for better access to thin breasts. Lesions accompanied by diffuse microcalcifications that are scattered throughout the breast also are difficult to target. The procedure may not be successful when a patient has only a vague change in tissue density and no distinct mass or lesion indicated by mammography. Lesions sometimes can be overlooked and the extent of disease may at times be underestimated with stereotactic techniques. If diagnosis remains uncertain after the procedure, surgical biopsy may be a patient's only option (8, 9). Stereotactic needle biopsy is a purely diagnostic procedure. Unlike surgical excision, which involves the removal of an entire mass or lesion, needle biopsy is not therapeutic (10). It is possible to completely remove a small lesion with core biopsy. If all or part of a lesion is removed, intentionally or not, the physician should place a percutaneous clip to mark the lesion site. This will facilitate locating the site again if the sampled tissue is malignant and requires treatment (9, 11).

### Advantages

A major advantage of stereotactic-guided needle biopsy is that it is an outpatient procedure and significantly less invasive than surgical biopsy. According to a study by Panizza et al, MR-guided stereotactic biopsy in particular is relatively fast and simple. The procedure took approximately 45 minutes on average and proved to be safe and accurate compared with interventional breast procedures performed under mammography and ultrasound guidance (12). This decreases patient anxiety and increases cost-effectiveness. Compression of the incision area typically is sufficient to stop any bleeding, although some patients may need to wear a pressure garment, particularly after a procedure using a vacuum-assisted device (7).

Needle biopsy is more cost-effective than surgical biopsy (7, 13) particularly to examine lesions associated with moderately suspicious mammograms. In a study by Wolf et al, data were analyzed from 182 nonpalpable lesions (American College of Radiology Breast Imaging Reporting and Data System, or BI-RADS, category 5) sampled in 178 patients over 5 years using stereotactic needle biopsy or surgical biopsy. Use of stereotactic biopsy was associated with fewer total surgical procedures per lesion (1.29 +/- 0.05 vs 1.8 +/- 0.05, respectively;  $P < 0.05$ ). The study found that stereotactic breast biopsy as a first biopsy procedure in patients with suspicious mammograms was associated with improved pathologies and the need for fewer surgical procedures and should be considered the preferred method of diagnosis over surgical biopsy (14).

Lieberman et al compared several different types of stereotactic-guided needle biopsies and showed that 11-gauge, vacuum-assisted biopsy was significantly more likely to spare a surgical procedure and also yielded higher cost savings than either 14-gauge, automated core biopsy or 14-gauge vacuum-assisted biopsy. In addition to being less invasive and more cost effective, needle biopsy also takes less time than surgical biopsy and is more comfortable for the patient (15).

The samples are labeled and prepared for the pathology department. Samples also may be examined with **specimen radiography**, especially those with microcalcifications.

### Patient Care

Immediately after the procedure, the technologist should apply pressure to the lesion and the biopsy path to stop any bleeding from these areas. The incision site then is cleaned and dressed, and the incision is closed with a sterile bandage. A cold compress can be used if swelling is excessive. If mild pain or any discomfort persists, the patient can use over-the-counter pain relievers (11).

### Complications

Complications associated with needle biopsy are rare and include hemorrhage (especially if a blood vessel is traversed), vasovagal reaction, wound infection or hematoma (6, 7).

### Conclusion

Stereotactic breast biopsy is indicated for women with BI-RADS category 4 breast lesions and has several advantages over surgical biopsy, including a significantly less invasive approach, decreased patient anxiety and pain, quicker recovery time and cost-effectiveness (7). Furthermore, because most breast findings are benign, needle biopsy can spare women with such findings from having to endure a surgical procedure (9).

Like all radiologic modalities, stereotactic breast biopsy has its limitations and may not be appropriate for all women, including those with insufficient breast tissue, augmented breasts or who are pregnant or breast-feeding. Complications associated with needle biopsy are rare and include hemorrhage, vasovagal reaction, wound infection or hematoma (7, 9).

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