Breast Cancer in Turkey

Clinical HistopathologicalCharacteristics and Standard Prognostic Factors

An Analysis of Data from the National Breast Cancer Database (UMKVT) of Turkish Federation of Breast Diseases Societies (TMHDF)

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Dear Reader,

As a breast surgeon, I always asked an important question to myself in all scientific meetings: Why do we not have a regular breast cancer registry in Turkey and why do we not have statistics and data for our patients? We were trying to conduct and publish clinical studies using data from the patient database at the Breast Unit, which we established back in 1986 when I was the Chief Resident at General Surgery Department of Istanbul Medical Faculty. But it has now become a scientific obligation to create a "National Breast Cancer Database," collecting data of breast cancer patients from different regions and cities across the country.

The project, "National Breast Cancer Database (UMKVT)," which I had presented in December 2004 during the Board Meeting of the Turkish Federation of Breast Diseases Societies (TMHDF), originally initiated during the 1st Annual Meeting of the World Society for Breast Health in Istanbul, 2001, was accepted and a decision was taken to implement the project. We contacted PleksusBilişimTeknolojileri and signed an agreement with them for the federation.After intensive studies, a committee formed by Pleksus and the federation determined the type of information and questions that the breast cancer registry would need to contain. Special courses were organized for associates at centers that would take part in the registry. The National Breast Cancer Database was officially launched for use in May 2005, with both an online and offline version. Taking account of the numerousness of questions and the difficulty of using the software, a number of changes were made to the database in 2009, which were published in a book, designated Version 2. Thanks to these modifications the registry became faster and more user-friendly. Upon a decision of the Federation Board of Directors, it was decided to compile the information in a book and make it available to national and international science community. I do hope and believe that this book, which will be also translated to English, will represent a significant contribution to accessing scientific data on women in Turkey who were diagnosed with and are being treated for breast cancer.

Pruning and analysis of data presented in this book was performed by Dr. NilüferÖzaydın from Family Practice Department of Marmara University Medical School. Prof. Dr. BahadırGüllüoğlu and Dr. ErsinSelçukÜnal also made valuable contributions to preparing this book.

Scientists typically neglect their spouses and children throughout their careers, but this does not change the fact that they are our greatest source of support, allowingus to continue producingour work. Therefore, they do have a large contribution in our work, which we are able to create through long efforts, and for that I extend my gratitude to our families.

I also thank our former and new colleagues on the board of directors who gave their full support for all scientific projects since the inception of our Federation, and**Novartis Oncology Turkey**who provided financial support to our project from day one, and female patients whose data we have used in this project.

Sincerely,

Prof. Dr. VahitÖzmen

Editor

Overview

Breast cancer is the most common type of cancer and the leading cause of cancer deaths in womenin Turkey, as elsewhere around the world. However, detailed and systematic demographics, data on clinical and pathological properties, and therapy data on women with breast cancer were largely unavailable in Turkey until now. This report is intended to provide an analysis of clinical and pathological data on women registered in the National Breast Cancer Database (UMKVT), established within Turkish Federation of Breast Diseases Societies (TMHDF) and available for use in Turkey since 2005, and to catalyze discussion of the findings in view of scientific literature. The part of the analysis covering therapy and follow-up data is currently being compiled in a second book.

Clinical and pathological data on breast cancer patients registered online in the database from May 01, 2005 were investigated. Patients diagnosed with breast cancer were sorted by gender. Parameters examined in female patients included age, menopausal status, distribution of clinical and pathological stage, histological type of invasive cancers, tumor diameter, histological grades, regional lymphatic stage, estrogen, progesterone, HER-2 receptors and molecular subtypes. Analysis results of these parameters were compared with literature data and discussed.

A total of 13,240 cases operated for breast cancer since April 07, 1992 were included in the study. 99% of the subjects were female, and 1% were male. Female patients with breast cancer whose requisite parameters had been completely entered in the database were included in the analysis. The mean age of diagnosisin female patients with breast cancer (including those diagnosed with ductal carcinoma in situ) was 51.6 (±12.6; range 12 – 97), 17% of whom were younger than 40 years of age, and 45% were premenopausal. According to an analysis of age groups at diagnosis, the frequency of cancer peaked at the 45 – 49 age group with 16.7%, declining to 7.6% in the 65 – 69 age group, and then rose again. According to histopathological examination results, 5% of patients had ductal carcinoma in situ (DCIS), and 95% invasive breast cancer. 78.7% of invasive breast cancers were invasive ductal cancers, 7.8% were invasive lobular cancers, 9.8% were invasive mixed cancers (invasive ductal + invasive lobular), and 4% were other histological types (e.g. inflammatory, intracystic papillary, mucinious, etc.). 50% of invasive breast cancers were histological grade III. According to an analysis of pathological stages of all breast cancers (stage 0 – IV), 55% were stage 0, 27% were stage I, 44% were stage II, 21% were stage III, and 3% were stage IV breast cancers. 75% of invasive breast cancers were stages I & II, and 25% were stages III & IV. The mean tumor diameter was 2.5 cm (± 1.6; range 0.1 – 20 cm). 50% of women with invasive breast cancer were pN0, 28% were pN1, 15% were pN2, and 7% were pN3, of whom 70% were estrogen positive, 59% were progesterone positive, and 23% were HER-2 receptor positive. A subtype analysis of tumors showed that 62% were type luminal A. This was followed by subtypes luminal B (15%), triple negative (15%), and HER-2 positive (8.5%).

Turkish Federation of Breast Diseases Societies (TMHDF)

Breast Cancer in the World

Breast Cancer in Turkey

Turkish Federation of Breast Diseases Societies (TMHDF)

Breast Societies of Istanbul, İzmir, Bursa and Ankara came together and formed the Coordination Council ofBreastSocieties (MDKK) in 2001, which was later joined by nine more societies, bringing the membership to 13 societies, and the council adopted the designation of federation in 2007. The Federation gained the entitlement to precede its title with the word 'Turkish' since October 03, 2011.

The founding purposes of the Turkish Federation of Breast Diseases Societies (TMHDF) include bringing together all scientific societies and holding all scientific events (e.g. congresses, consensus meetings, conferences, educational courses, etc.) in Turkey pertinent to breast disease, initiating multidisciplinary studies, publishing a scientific journal, publishing books on breast disease, creating and maintaining a national registry for breast cancer, collaborating with national and international bodies to enhance the scientific level for early detection and treatment of breast diseases, collaborating with the Anti-cancer Bureau of the Ministry of Health (KSDB) to conduct joint projects for screening, early detection and effective treatment of breast cancer taking account of national economic conditions, educating the general public and in particular the target audience of women on breast cancer, and raising awareness of breast cancer.

TMHDF completed numerous projects, and is currently working on developing new ones toward the purposes listed above. Since its inception, four National Congresses, five National Consensus Meetings, and numerous regional meetings, conferences, and educational courses were held. The Journal of Breast Health, published since 2005, was included in the publications index by TÜBİTAK and EBSCO Publishing, and is currently awaiting admission to Pubmed. The Federation is a member of various international breast organizations, including World Society for Breast Health (WSBH) and Senologic International Society (SIS), and serving on their boards of directors.

To achieve another one of its objectives, TMHDF joined hands with the Anti-cancer Bureau of the Ministry of Health (KSDB) and began holding "National Breast Cancer Educational Courses," aiming to maximize the knowledge and skills of physicians working at Cancer Early Detection, Screening and Education Centers (KETEMs) and general surgeons, pathologists, radiologists, medical oncologists and radiation oncologists working at state hospitalsin breast cancer to provide patients with the best screening, diagnosis and treatment possible. To date, 10 courses covering 61 provinces were organized, reaching and certifying more than a thousand physicians.

TMHDF initiated many multidisciplinary studies, some of which were presented during international congresses and published in journals (1,2,3), and several studies are currently ongoing.

Nationwide campaigns, such as MaviBisiklet*(Blue Bicycle)*, HareketeGeçHikayeniGönder*(Take Action, Send in Your Story)*, and Annemle Biz KanseriYeneriz*(Mom and I Will Beat Cancer)*, were held with support from other sponsors to raise public awareness of breast cancer, particularly in our target female audience.

The National Breast Cancer Database (UMKVT) is another important project which is currently being executed by TMHDF. The decision to implement this project was taken by the federation's board of directors in December 2005, and the services of a professional software developer (Pleksus) was retained for developing and implementing the software application. Entry of patients in the registry began in May 01, 2005, and data of approximately 19,000 patients were entered as of August 2012.

Breast Cancer in the World

Breast cancer is the most common type of cancer in women, accounting for approximately 23% of all women's cancers (4). According to data from the International Agency for Research on Cancer (IARC), an organ of the World Health Organization (WHO), approximately 1,380,000 new cancer cases were diagnosed in 2008. Considering the whole of cancer cases, this figure is second highest after lung cancer (10.8%). Although incidence of breast cancer is higher in the developed world, the number of new cases of breast cancer detected in 2008 were the same in both groups, i.e. approximately 690,000, due to the population of the developing world being four-times larger than that of developed countries (4). Breast cancer incidence based on the development level of countries is approximately <20 / 100,000 in impoverished countries (19.3 / 100,000 in Eastern Africa), 89.7 / 100,000 in Western Europe and other developed countries (excluding Japan), and 40 / 100,000 in other developing countries, including Turkey (5). Approximately 4.4 million women worldwide were diagnosed with breast cancer over the past five years, making breast cancer the most prevalent type of cancer in the world (6).

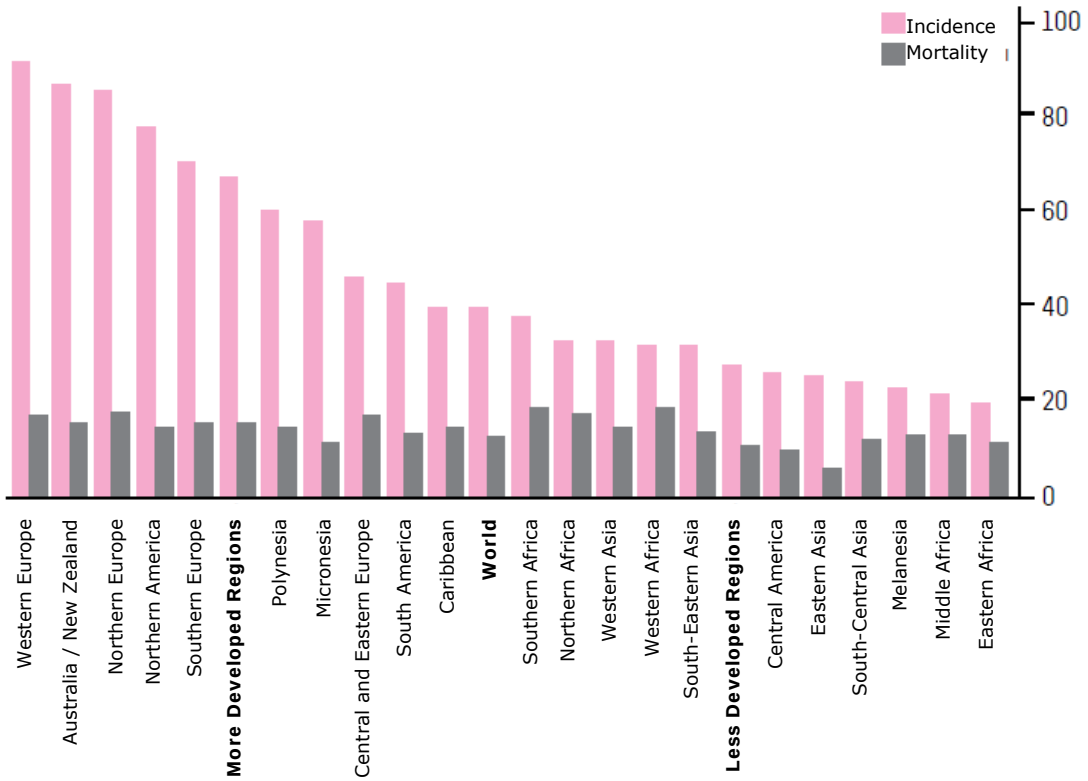


Figure 1.Breast cancer incidence in various countries, and in the more developed and less developed world (Globocan 2008).[7]

Breast cancer incidence varies between more developed and less developed countries (Figure 1) (7). Although breast cancer is more frequent in the developed world, the incidence rate of the disease has declined in these countries over the past decade (Figure 2). Main reasons for this decline include detection

ofprecursor lesions of cancer through community-based screening programs, broadly used for over 50 years (DCIS, ADH), the increasing number of women receiving prophylactic mastectomy, the use of aromatase inhibitors and estrogen receptor blockers such as tamoxifen, raloxifene, and exemestane, and specifically the significant reduction in hormone replacement therapy over the past decade. Particularly after the publication of results from a Women Health Initiative (WHI) study in 2002, use of HRT declined by 80%, and breast cancer incidence by 12% in the US (8,9).

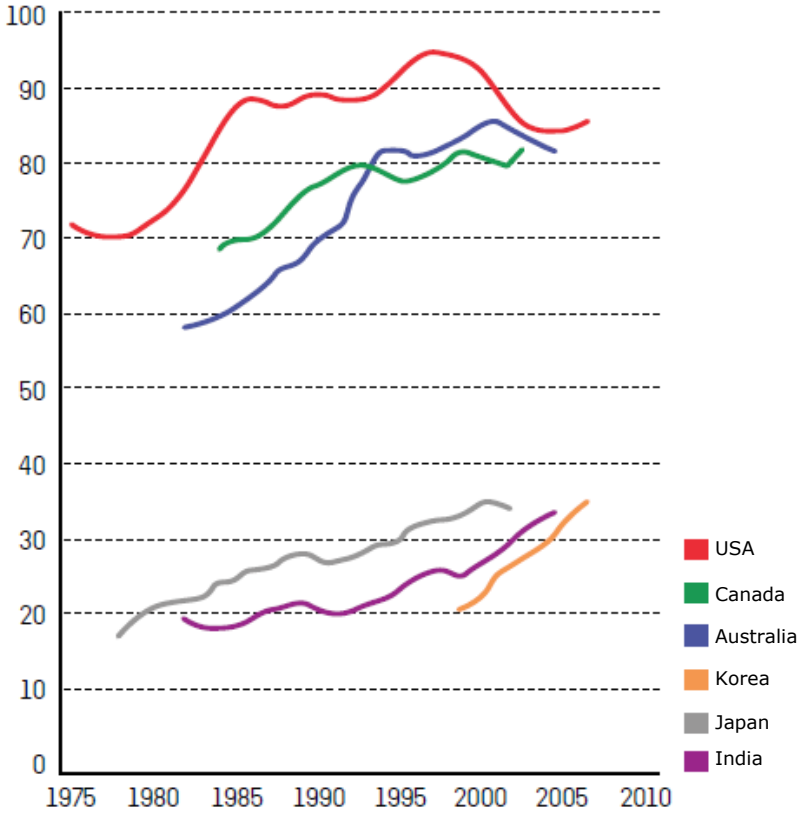


Figure 2. Breast cancer incidence declined in the developing world from 2000s, but rose in some Asian countries. [7]

The incidence of breast cancer is declining in developing countries, but rising in medium- and low-income ones. Reasons of this rise include Westernized lifestyles, changes in reproductive life [not giving birth, having fewer children, giving birth at a later age (>30), not breastfeeding, overweightness, changes in eating habits, higher exposure to hormones (hormone replacement therapy, early menarche, late menopause, use of oral contraceptives, etc.] and other factors possibly associated with industrialization (6,10). Studies show a growing frequency of breast cancer in women emigrating from countries with lower incidence rates to countries with higher incidence rates (e.g. from China or Japan to the US or Canada), and in their descendants, which supports the Westernized lifestyles argument (10). Despite low incidence of breast cancer in impoverished countries, the lack of capabilities for early detection and effective therapy usually results in the disease being detected at the advanced stage and hence higher mortality rates (11).

Although breast cancer is more frequent in the developed world, mortality rates are far lower [mortality / incidence rate of 0.30] (4). With generalized availability of screening programs, education and increased awareness, the percentage of non-palpable breast cancers reached 75%, with lower rates of axillary involvement. In these countries, mortality rates continue to decline, thanks to early detection and effective therapy (see Figure 3). According to a 2008 IARC analysis, breast cancer ranks in fifth place as a cause of death among all cancer

types, and in first place in women. Similarly, in that year 458,000 women died worldwide from breast cancer, 58.7% of whom were in lower- or medium-income countries [mortality / incidence rate of 0.43] (4).

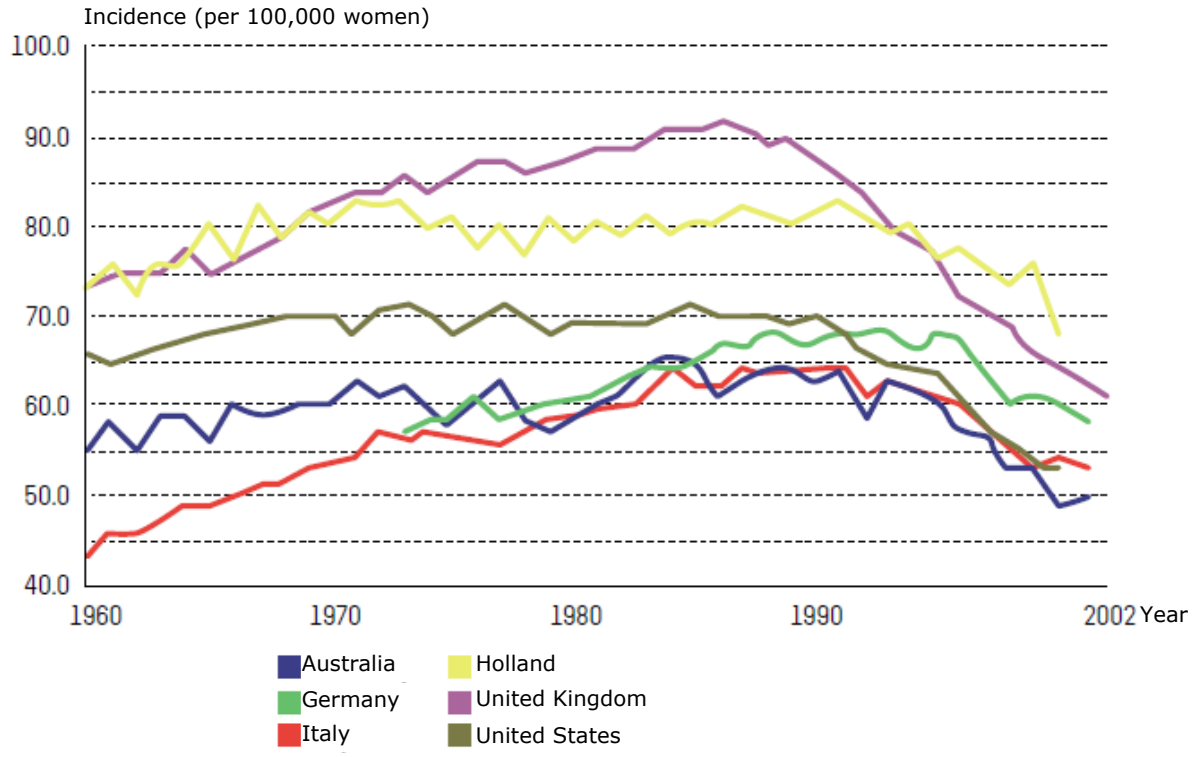


Figure 3. Breast cancer mortality rates are declining in the developed world (age-standardized rate per 100,000 women).[4]

Increasing breast cancer incidence with a high mortality rate in developing countries and in some developed Asian countries may be explained by a lack of organized use of community-based screening techniques, cancer not being considered as a priority health concern, low breast cancer awareness, lack of education, inadequate availability of diagnostic and therapeutic means, diagnosis at the advanced stage, and inadequate and ineffective treatment (see Figure 4).

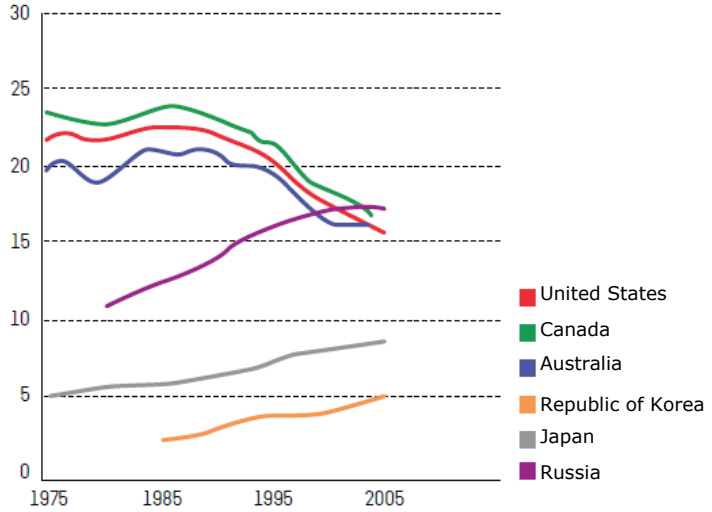


Figure 4. Breast cancer mortality rates are declining in some developed countries (age-standardized rate per 100,000 women), while they continue to rise in Asian countries and in the developing world.[4]

The Breast Health Global Initiative (BHGI)

Cancer has surpassed infectious diseases, tuberculosis, and HIV syndrome, becoming the second leading cause of death in lower- and medium-income countries. Despite the misconception that breast cancer is a problem of developed countries, most cancer deaths are occurring in developing countries (4), where breast cancer incidence is increasing by 5% every year (5,6,11). Although global breast cancer incidence has increased by approximately 0.5% annually since 1990, the rate of increase was 2- or 3-fold in Japan, Singapore and Korea. And Chinese records show an incidence increase rate of 20 to 30% over the past decade (4). Although developing countries have relatively younger populations, breast cancer ranks first in terms of incidence and mortality rates, and is responsible for 20% of all women cancers and 12.7% of annual cancer deaths in those countries. In the years ahead, breast cancer incidence growth is expected to continue in lower- and medium-income countries mainly due to: 1. Increased life expectancy, 2. Similarities with Western Societies in certain reproductive and lifestyle characteristics (6,11). Between 2002 and 2020, global breast cancer incidence and mortality rates are expected to increase by 50% for demographical changes alone. Given such increase, breast cancer incidence in developing countries may be expected to grow by 55%, and mortality rates by 58%, by year 2020 (11). However, these statistics are not representative of the actual breast cancer incidence since regular data collection is not possible in lower- and medium-income countries due to unavailability of robust registries. Despite the advances in diagnosis and treatment of breast cancer, lack of means continue to reduce early detection, screening and treatment possibilities in impoverished countries. Thus, patients can be diagnosed at later stages of the disease, where therapeutic options are limited, causing higher rates of mortality and morbidities (4,11). A 2011 Indian study found that 50 to 70% of breast cancer patients were in the locally advanced or metastatic stage of the disease at diagnosis (6,11). In comparison, according to US and European cancer registries, the percentage of locally advanced or metastatic breast cancers was 44% and 36% in 1990 and 1992, respectively, which declined to below 20% in recent years (12,13).

A lack of adequate healthcare infrastructural means and resources, required for early detection, screening and treatment, is driving up the mortality rate of breast cancer. Wealthy countries have in place evidence-based guidelines for early detection, screening and treatment (14,15), which have limited use for lower- and medium-income countries. Developing and implementing international evidence-based guidelines for these countries represents another important step. The Breast Health Global Initiative (BHGI), co-sponsored by Fred Hutchinson Cancer Research Center and Susan G. Komen for the Cure, aims to develop evidence-based guidelines that take account of the economic and cultural structure to improve breast cancer diagnostic and therapeutic outcomes in lower- and medium-income countries. BHGI held its first two meetings in Seattle (2002) and Maryland (2005), USA, to highlight healthcare differences between lower and medium-income countries and wealthy ones, and evidence-based resource sharing for breast cancer. Early detection, screening, treatment and healthcare system guidelines were developed through evidence-based consensus panels, modeled after National Comprehensive Cancer Network (NCCN) (16-19). BHGI guidelines aim to educate Health Ministry staff, politicians, directors, and administrators developing and allocating resources for diagnostic and therapeutic programs for breast cancer in lower- and medium-income countries. The 2007 BHGI summit held in Budapest saw the development – and subsequent publication – of formulas and metrics for the guidelines which were developed (11,19). The fourth meeting, titled "Optimizing healthcare delivery,"

was held in Chicago, 2010, and the fifth one in Vienna, between October 3 and 5, 2012, under the title Guidelines for International Breast Health and Cancer Control – Supportive Care and Quality of Life.

Cancer Registries

A most important point for cancer control is to ensure national cancer registries are maintained in a complete and accurate manner. Prioritizing and robust decision-making on development of national health policies, creation of strategic plans, and allocation of limited resources cannot be possible unless statistical analyses based on accurate data are available.

Main constituents of "cancer control" are prevention, early detection, effective treatment, rehabilitation, and palliation. Cancer registries are the starting point of cancer control. In a nutshell, acancer registry is the whole of all studies performed to collect information about cancer cases occurring in a community. It is essential to investigate, and to manage and rectify adverse effects of malignancies on patients and the society. Collecting information on cancer diagnosis, development, attributes, treatment and patient survival can be possible only through a multidisciplinary effort.

Regular keeping of cancer registries allows investigation of factors causing cancer, and developing ways to protect against them. Approaches for diagnosis and treatment of cancer patients, and their outcomes may be demonstrated by analyzing the data collected; and diagnostic and therapeutic approaches and effectiveness analyses results may be compared between specialists, healthcare providers and/or geographical regions, providinginput for the development of national screening, diagnostic and therapeutic guidelines, and enabling determination of regional needs (e.g. human resources, diagnostic and therapeutic tools and equipment, medicines, etc.) for an optimal therapeutic approach and appropriate allotment of resources in this disease group, which requires broad multidisciplinary collaboration. Another important point is that, it may determine the effects of various therapeutic approaches on patient quality of life to enable improvements.

Evolution of Cancer Registries

The oldest modern cancer registry was created in 1929, in Hamburg (20). The program stated that public health and economic aspects, as well as medical and scientific ones, must be also taken into consideration in cancer control. The first community-based cancer registry was launched in 1935 in the USA. The Surveillance, Epidemiology and End Results (SEER) program began collecting data in 1973 within the National Cancer Institute (NCI), as the official source of information in the US for cancer incidence and survival data (21). SEER collects and publishes cancer data covering approximately 28% of the US population.

The Danish Cancer Registry was established in 1942 by the Danish Cancer Society. This excellent program covers not a single city, but the entire national population (22).

The International Association of Cancer Registries (IACR) was founded in Tokyo in 1966, one year after the launch of the International Agency for Research on Cancer in 1965 by the World Health Organization as a private cancer research center (23). The Agency collaborates with IARC to help member states create their own cancer registries and to publish analyses on cancer incidence and therapy outcomes. Currently, there are approximately 200 population-based registriesmaintained around the world.

Detection of asymptomatic, non-palpable breast cancers via screening programs allows patients to continue living healthy lives without organ loss. Cancer registries also play an important role for the evaluation of screening programs. Breast cancer incidence and increase rate data obtained will play an important role in determining the necessity, effectiveness and economic viability of mammographic screening programs. With increasing number of breast cancer cases detected early via screening programs, the incidence of breast cancer will also increase, but mortality rates will decline. In other words, the main goal of cancer registries is to help reduce breast cancer deaths. Cancer registries will determine mortality rates, distribution of stages, and the number and percentage of interval cancers (i.e. cancers not reported during a screening program, but detected in a subsequent mammographic checkup), allowing comparisons between screened vs. non-screened women to demonstrate the relevance of screening programs. By a decision adopted in 1994, the European Parliament recommended countries to develop registries in their territories (25).

Cancer Registries, Survival and Quality of Life

Cancer registries also contain information on cancer deaths, allowing calculation of community-based survival rates, which are highly important for planning patient care and medical services. Conducting clinical trials is the only way to determine whether a particular therapy administered to cancer patients is better than others. It may be misleading to derive survival conclusions based on results from smaller-scale studies with selected patients from a single center. However, data from cancer registries can be used to determine the survival effect of a particular therapy, by examining disease-free and average survival rates in patients who were and were not treated with the therapy in question, which provides insights into the functioning and quality of the healthcare system as well.

Cancer registries also allow determination of secondary cancers which may develop due to radiotherapy and/or chemotherapy, and enable gaining information on tumor prevalence and statistical analysis of survival rates with tumors of different stages using appropriate and applicable standard methods (e.g. TNM). However, it is considered a drawback of cancer registries that they do not contain metrics for quality of life.

Cancer registries contain demographics and clinical and pathological findings inpatients, making them a suitable resource for numerous studies in biomedical sciences. In Turkey, “death certificates” and “hospital records” do not contain patient information of sufficient accuracy, integrity, currency and validity (25), which highlights the need for a “Central Cancer Registry.”

It is also a top concern to ensure that cancer registries incorporate sufficient safeguards to protect “personal privacy” of patients. Patients enrolled in registries are given assurance that their information will be maintained confidential and used solely for scientific purposes and not disclosed to anyone, and then they are asked to sign a consent form.

In cancer registries, methods of data collection take three forms: active, passive and linkage (25). In the active approach, cancer registry staff identifies cancer cases and compiles information on them according to international standards of cancer registries, in other words the data is collected from the source. In the passive approach, information on cancer cases are sent to the registry center by medical staff. In the linkage approach, data otherwise collected and converted to digital form are pooled at the central registry via the Internet.

The National Breast Cancer Database (UMKVT) of the Turkish Federation of Breast Diseases Societies uses the active and linkage approaches for data collection. Breast cancer patient data identified at intermediate centers are entered in the computer online and/or offline by appropriately trained physicians or cancer registry staff, pooled at the central registry, and submitted to the registry officer in the form of weekly or monthly bulletins.

Cancer Registries in the Developing World

Due to high infant mortality rates, nutrition disorders and infectious disease mortalities, "cancer registries" are considered somewhat a luxury in less-developed and developing countries, which thus have inadequate recording of medical services. Moreover, lack of trained medical professionals, education, awareness, screening programs, infrastructure, and diagnostic and therapeutic insufficiencies contribute to late detection, deficient treatment and/or treatment errors. Substantial imparities exist between rural and urban areas and regions in terms of distribution of medical services. Thus, data from large cities and urban centers where cancer registries are maintained in a more orderly manner cannot be considered representative of the entire population.

Lower- and medium-income countries have critical deficiencies in their basic healthcare services, including: 1. Physicians are overloaded with work and lack the time to allocate for a registry; 2. Cancer data collected is not accurate, due to diagnostic and therapeutic insufficiencies; 3. Barriers in accessing care; 4. Lack of post-mortem examinations; and 5. Healthcare professionals, in particular physicians, do not believe in the necessity of registries, and hence do not make an effort (25).

High rates of interregional migration precludes generating adequate demographic data, and information available is often incomplete. Duplications are common in software, due to the data entry errors or same patient's presenting at multiple centers.

In Turkey, the number of staff trained in cancer registry operations is extremely small. Deriving usable and reliable conclusions / deductions from data entails obtaining, pooling, analyzing, and interpreting data. Thus multidisciplinary collaboration of experts holds crucial importance.

Patient monitoring is impossible, or at best inadequate, in developing countries. There are numerous difficulties that prevent physicians from contacting patients, and patients contacting physicians, via mail or telephone. Sufficient funding is not available, nor is there a sense of urgencyto establish the infrastructure necessary for a cancer registry.

Because healthcare institutions in those countries have not undergone the required level of institutionalization, patients must seek medical care from both private and public hospitals. It is virtually impossible to collect cancer records from such multiple, non-institutionalized centers. It is also crucial to have the necessary regulations in place. Yet, despite regulatory requirements, reports are often omitted.

Diagnosis and treatment of cancer is a costly operation which places a large burden on our national economy. Cancer registries identify common cancers and diagnostic stages in the country, helping to take appropriate preventive measures, develop the national health economy, and ensure appropriate and effective use of resources.

Cancer Registries in Turkey

Unfortunately, cancer registries were introduced in Turkey far later than in developed countries (26). Although cancer control efforts began to institutionalize in 1940s, the first cancer registry was launched in 1982, by ministry circular notice #5621 of 14.09.1982, which included cancer as amust-be-reported disease. To facilitate conduct of registries, an "Anti-cancer Bureau" was established in 1983, by Decree Law #181. The Anti-cancer Bureau is responsible for cancer control, and its main responsibilities include collecting cancer records in a high-quality, reliable and accurate manner.

In 1991, the "İzmir Cancer Incidence and Data Collection Project" (İKİP) was launched by a protocol signed between Turkish Ministry of Health, Turkish-American Center for Healthcare Research, and Ege University. İzmir Cancer Registry (KİDEM), established within Provincial Health Directorate of İzmir on March 13, 1993, was commissioned to coordinate the project work. The project, initiated by establishing hospital-based cancer registries at certain hospitals, aimed to provide a means for centrally recording, monitoring and evaluating cancer cases in İzmir province, and constituted the core of KİDEM.

In 1995, İzmir Cancer Registry was admitted to World Health Organization (WHO) International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR), and in 1997 to European Network of Cancer Registries (ENCR). In 2004, it joined the Unified Cancer Registry Project, conducted by Middle East Cancer Consortium (MECC), of which Turkey is an official member. In 2002 and 2008, IARC used İzmir Cancer Registry data for Globocan, which served as an endorsement of the quality of data from the province of İzmir.

After İzmir, the KSDB included 12 more provinces (Edirne, Trabzon, Samsun, Erzurum, Eskişehir, Ankara, Antalya, İzmir, Kayseri, Şanlıurfa, Adana and Bursa) in the active cancer registry program. At present, Kocaeli (cancer deaths are the leading cause of death in Dilova area) and Van (to represent the EasternAnatolia region) were added to these provinces, bringing the total number to 14. The cancer registry program continues to be run in those provinces.

Cancer Incidence in Turkey

As elsewhere around the world, cancer deaths rank in second place with 22% after deaths from cardiovascular disease. However, cancer is among preventable and manageable diseases. An IARC study reported that cancer incidence would increase approximately 2-fold by 2030. It is worth noting that 75% of this increase will occur in less-developed and developing countries, including Turkey. To ensure control of cancer, these countries must increase their spending on cancer screening, detection and treatment, which mostly accounts for 5% of their national budgets, and in particular implement well-planned primary, secondary and tertiary mechanisms.

Dr. Eser, who studies this issue, explains cancer incidence predictions for Turkey under three headings (25):

1. Datasets 1993 – 1994 and 1996 – 2000 from İzmir Cancer Registry, and dataset 1993 – 1996 for childhood cancers are available (27). The initial results from İzmir Cancer Registry covering years 1993 and 1994 were published in 2001 (28), which indicate a cancer incidence of 157 per 100,000 women and 94 per 100,000 men. Breast cancer is the most common type of cancer in women with an incidence of 24 per 100,000.

According to the 1996 – 2000 dataset presented by Dr. Eser for İzmir, incidence of cancer in women and men increased to 109 per 100,000 and 173 per 100,000, respectively (25). The six most common type of cancer in women are breast cancer, colorectal cancer, uterine cancer, cervical cancer, lung cancer and ovarian cancer. The breast cancer incidence rate has increased by 7.6% over the past five years (24 vs. 31.6 per 100,000).

2. Cancer Registry data: Although these have low validity (completeness and scientific accuracy) due to their maturing nature, they provide a ballpark figure of cancer incidence in Turkey and are presented here as a preliminary draft (25).

Registries in Antalya, Trabzon, Samsun, Eskişehir, Edirne and Edirne were audited in 2006, and data from Antalya, Trabzon, Samsun and Eskişehir data were processed and analyzed as a preliminary draft. According to these data, breast cancer incidence in these provinces are 28.6, 23, 33.3 and 24 per 100,000, respectively.

Cancer statistics, created based on latest data belonging to year 2005 from MoH Anti-cancer Bureau active registry were posted on their official website (26). According to said statistics, cancer incidence in Turkey rose to 173.8 per 100,000 from 58 per 100,000 in five years, representing almost a 3-fold increase (see Figure 5). Interpretation of this data should, however, take account of the questionable accuracy of data from previous years.

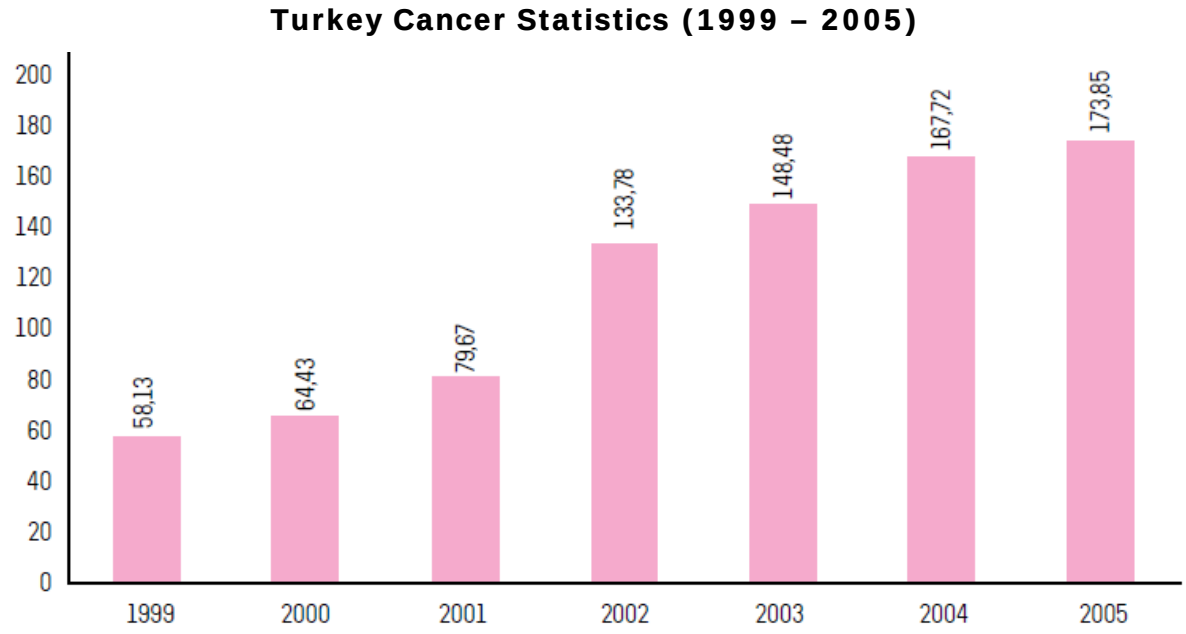


Figure 5.Increase of cancer incidence in Turkey over years.[26]

Looking at distribution by genders, we see that incidence of cancer in males is 30% higher compared to women (see Figure 6).

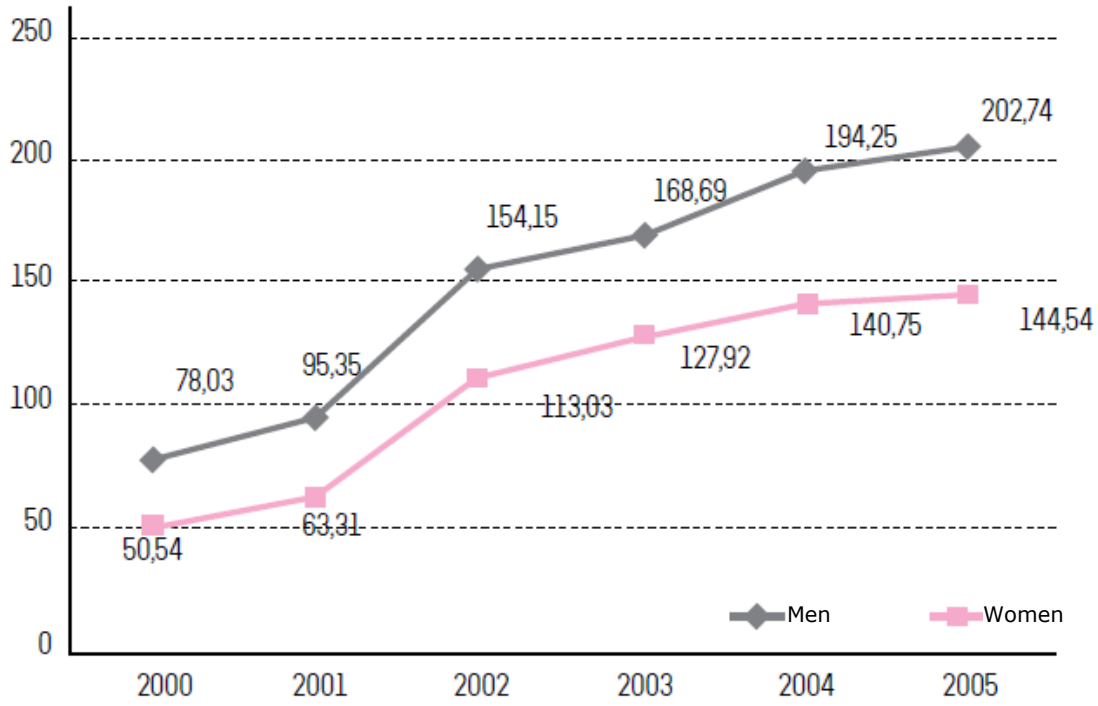


Figure 6. Cancer incidence in women vs. men in Turkey (2000 – 2005).[26]

In Turkey, where smoking and tobacco use is very common, lung cancer is the most common type of cancer, accounting for 30% of all cancers; breast cancer accounts for 18% of all cancers (see Figure 7).

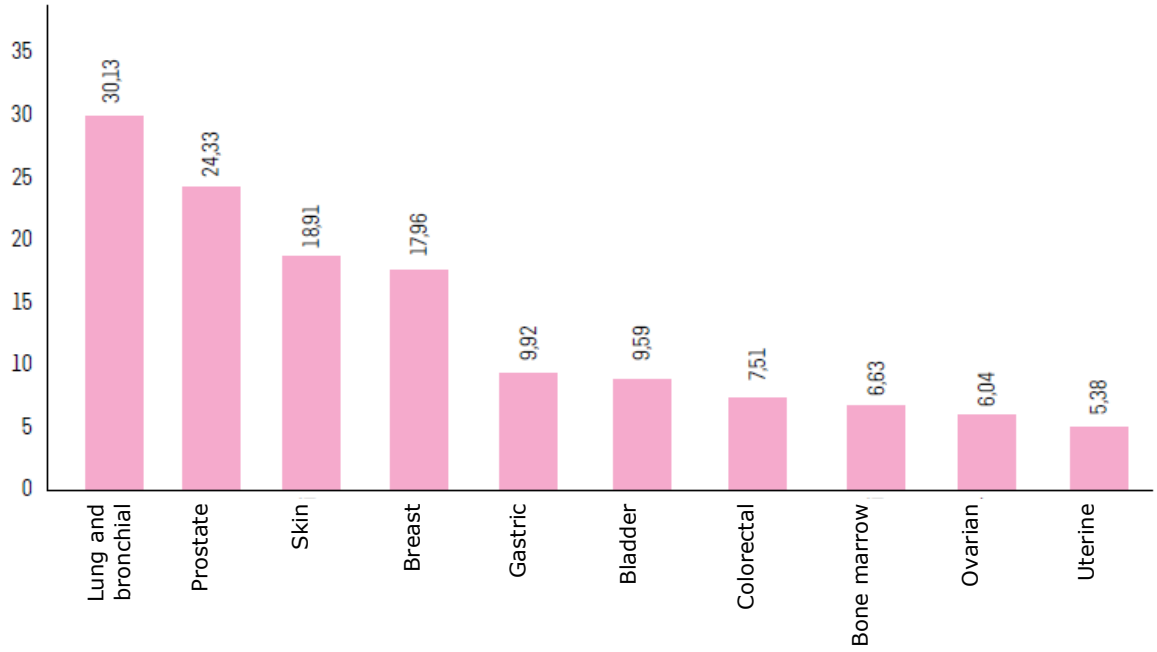


Figure 7. Most common cancer types in Turkey.[28]

Breast cancer is the most common type of cancer in women (35.47 per 100,000), followed by skin and thyroid cancers (see Graphic 8).

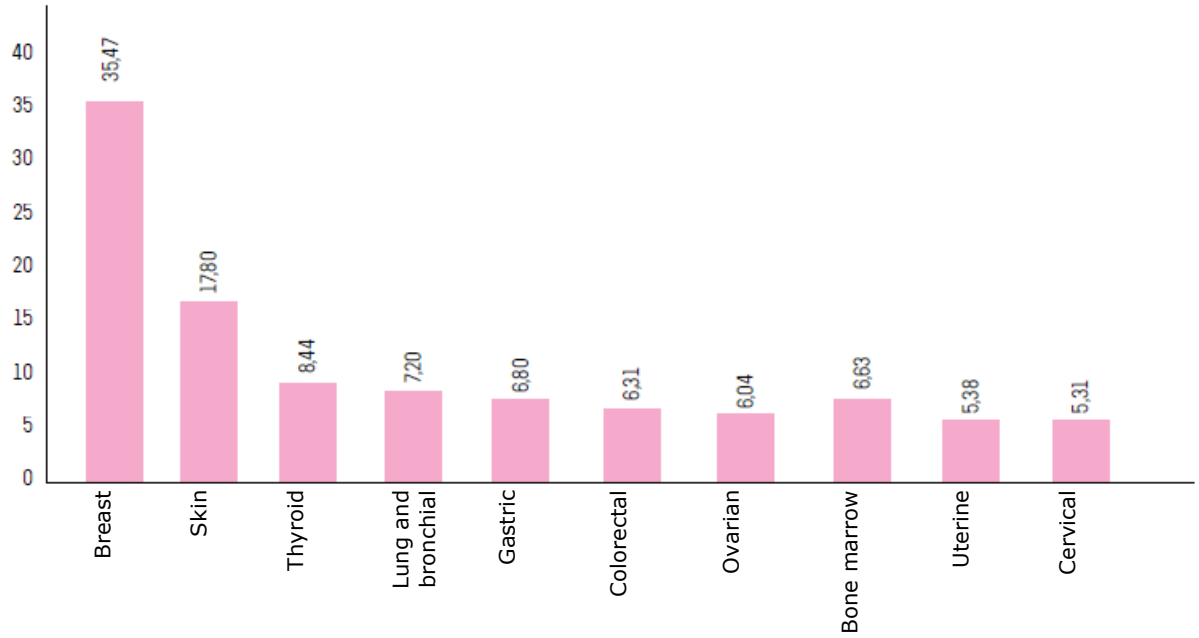


Figure 8.Cancers in women.[28]

3. Globocan data from International Agency for Research on Cancer (IARC) (29): Data collected across Turkey through passive reports were categorized by the International Agency for Research on Cancer (IARC) by gender, cancer type and age, based on seven geographical regions. Then, relevant populations were used to create a data pool, which was in turn used to determine relative frequency of cancers. According to IARC Globocan 2008 data, breast cancer frequency in Turkey was 28.3 per 100,000. Breast cancer constituted 25.6% of all women cancers, and was the leading cause of cancer deaths (17.6%). However, these figures are considered to be lower than the actual levels. In fact, according to 2006 Anti-cancer Bureau (KSDB) data, national incidence of breast cancer was 41.7 per 100,000 (age-standardized incidence is 37.6 per 100,000) (30). At present, these incidence rates are believed to have exceeded 50 per 100,000. Again, according to KSDB data, breast cancer accounts for 23.8% of all women cancers, followed by colorectal cancer and thyroid cancer (see Figure 9).

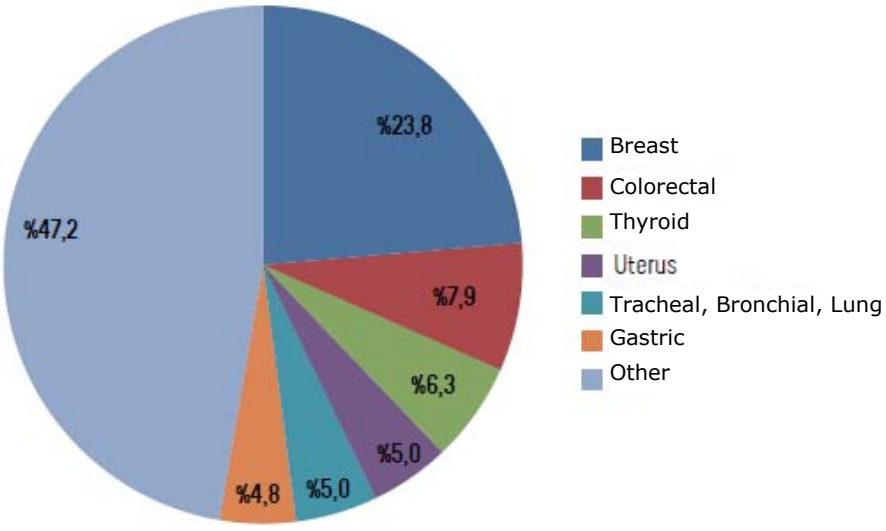


Figure 9. Most frequent women cancers by location (Turkey, 2004 – 2006).[30]

Breast Cancer Risk Factors in Turkey

A large number of studies were conducted in developed countries on breast cancer risk factors. However, there are few studies on this subject in lower- and medium-income countries where breast cancer incidence and mortality rates are steadily growing. Known risk factors for breast cancer are being female, age (> 50), being positive for mutant genes (BRCA1,2), familial history of breast cancer, overweightness (BMI > 25 kg/m^2), not giving birth, giving birth after the age of 30, using birth control pills for an extended period, receiving hormone replacement therapy for menopause, previous history of breast biopsy, and receiving radiotherapy on chest wall during childhood. In a comparative study we had conducted between 2000 and 2006 with 1497 women with breast cancer and 2167 healthy women, we looked at breast cancer risk factors among women in Turkey. We found that age (>50), history of abortion, body mass index > 25, first birth after the age of 35, and family history of breast cancer increased the risk for breast cancer, while longer education (> 13 years) and longer lactation period (> 12 months) reduced it (31). The correlation between undergoing an abortion and breast cancer remains highly-disputed. Some point to estrogen and changes associated with stress as the culprit. Having a longer education background may increase effectiveness of protection against breast cancer; and so may longer lactation, due to reduced estrogenic effect.

Patients and Procedures

The Database

The database was designed in cooperation with a professional software developer (Pleksus), as a computer application containing 576 parameters, and implemented in May 2005. The database has seven main interfaces: a. Identification, b. Biography, c. Clinical details, ç. Histological diagnosis, d. Surgical therapy, e. Postoperative pathology, f. Adjuvant therapy – chemotherapy, g. Adjuvant therapy – radiotherapy, ğ. Adjuvant therapy – hormone therapy, and h. Follow-up.

Timeframe

This paper covers an analysis of data from 13,240 patients, recorded from May 01, 2005 to May 01, 2011.

Data Entry

An announcement was made to centers affiliated with TMHDF, asking them to enter patient data in the database. Both prospective (online) and retrospective (offline) entry of data by centers were allowed. At each center committed to entering the data, a staff member was granted online access to the database. Following authorization, the responsible staff member was assigned a unique username and matching password, allowing data entry by centers. This report provides an analysis of patient data entered online into the UMKVT over a period of four years and three months.

Data Pruning

All data previously entered were reviewed both directly on an individual patient basis, and within individual institutions entering the data and across the entire database to weed out a. duplicates, b. inconsistent data, c. inappropriate data. Moreover, cases without name, surname, gender, birth date and age at diagnosis were excluded from the analysis.

Conclusions

Primary conclusions:

Distributions were analyzed in patients diagnosed with breast cancer by gender, age, and clinical and pathological stage, and in female patients by the histological type of invasive cancer, tumor diameter, histological grade, pathological regional lymphatic stage, estrogen, progesterone receptor, HER (c erb B2) expression and the subtype of breast cancer.

Secondary conclusions:

1. In female patients, the distribution of clinical and pathological stage, and in invasive cancers distribution of tumor diameter, histological grade, pathological lymphatic stage, estrogen and progesterone and HER-2 expression, and breast cancer subtype by age.
2. In female patients, the distribution of clinical and pathological stage, and in invasive cancers distribution of tumor diameter, histological grade, pathological lymphatic stage, estrogen and progesterone and HER-2 expression and breast cancer subtype by menopausal status.
3. In female patients with invasive cancers, the distribution of histological grade, pathological lymphatic stage and estrogen, progesterone and HER 2 expression and breast cancer subtype by tumor diameter.
4. In female patients with invasive cancers, the distribution of histological grade, and estrogen, progesterone and HER 2 expression and breast cancer subtype by pathological lymphatic stage.
5. In female patients with invasive cancer, the distribution of estrogen, progesterone and HER 2 expression and breast cancer subtype by histological grade.

Age analyses were conducted in groups of 10. The clinical stage was calculated and used in analyses based on clinical and radiological findings of the patient at presentation, and pathological stage based on the histopathological examination of the specimen removed during operation.

Histological types of invasive cancers were determined according to the classifications recommended by World Health Organization (32).

Tumor diameter, pathological lymphatic stage, histological grade, estrogen, progesterone and HER 2 neu expressions were analyzed only in patients with an invasive cancer confirmed by a final pathological report. Tumor diameter and axillary staging analyses were performed by categorization, as described in TNM classification (33). And histological grades were analyzed using 3 groups (grades I, II and III) based on modified Scarff Bloom-Richardson classification (33).

Estrogen and progesterone expressions were not only analyzed separately as positive or negative, but also by grouping as hormone receptor positive (either estrogen or progesterone positive) or negative (both estrogen and progesterone negative).

Molecular subtyping of cancer, a new approach in breast cancer patients, was performed in four groups of luminal A (estrogen or progesterone positive + HER 2 neu negative), luminal B (estrogen or progesterone positive + HER 2 neu positive), triple negative (estrogen, progesterone and HER 2 neu negative), and HER 2 positive (HER 2 group; estrogen and progesterone negative + HER 2 positive), and cases were analyzed based on these groups (34).

Analyses of cases were assessed based on their histological diagnosis (ductal carcinoma in situ or invasive cancer).

Statistics

Arithmetic mean, median, mode, minimum, maximum and standard deviation of continuous variables were determined. Kolmogorov-Smirnov test was used to evaluate the distribution of variables, Mann-Whitney U test to compare means of two independent groups, and Kruskall-Wallis test to compare means of more than two independent groups. Where appropriate, continuous variables were regrouped and separately analyzed based on their cut-off points and groupings. The correlation between categorical variables was assessed using the chi-squared test, taking 0.05 as the level of significance on Pearson chi-squared test.

Findings

It was found that since May 01, 2005, data for 13,420 breast cancer cases from 24 separate institutions were entered in the online database. The surgery dates of registered cases fell between April 07, 1999 and July 12, 2009 (see Table 1). After pruning, a total of 11,542 cases remained, whose data were valid.

Source of data	Number of patients	%	Case entry date
1. EgeUniversity Medical School	4076	30.8	07.04.1992
2. I.U. Medical School	3775	28.5	29.03.2007
3. Uludağ U. Medical School	1423	10.7	28.06.2005
4. Bursa MAMER Surgical Center	1308	9.8	18.06.2009
5. MoH Ankara Dışkapı TRH	611	4.6	12.04.2007
6. Dr. VahitÖzmen (individual)	530	4.0	09.07.2009
7. Kocaeli U. Medical School	300	2.3	22.03.2006
8. Dr. SavaşKoçak (individual)	267	2.0	10.04.2006
9. I.U. Cerrahpaşa Medical School	236	1.8	25.06.2009
10. Marmara U. Medical School	167	1.3	28.10.2005
11. A. Menderes U. Medical School	164	1.2	13.05.2009
12. Ankara U. Medical School	163	1.2	21.02.2007
13. Dicle U. Medical School	66	0.5	18.06.2009
14. Cumhuriyet U. Medical School	60	0.4	31.10.2005
15. Maltepe U. Medical School	39	0.3	29.04.2009
16. GüneydoğuAnadolu MD	24	0.2	10.03.2008
17. Çukurova U. Medical School	13	0.1	16.04.2009
18. Others	18	0.12	14.12.2007
TOTAL	13,420	100	
I.U.: Istanbul University, MoH: Ministry of Health, TRH: Teaching and Research Hospital, MAMER: Research Center for Breast Diseases, MD: Breast Society, DH: State Hospital			

Table 1.Data entry sites and number of patients with breast cancer.

However, in most of these cases it was found that data were missing on various parameters, and thus only those cases with sufficient data were included in the analysis. For the same reason, the number of cases varied on various parameters that were analyzed. The reason why the number of cases examined (n) during the evaluation of correlation between various variables was less than 11,542 is because the analysis excluded cases which had deficiencies in relevant data parameters.

The first entry in the database belonged to a patient that had been operated on April 07, 1992. Of the evaluated patients, 30.8 (4076) were reported from Ege University Medical School, 28.5% (3775) from Istanbul University Medical School, 10.6% (1423) from Uludağ University, and 9.8% from Bursa Research Center for Breast Diseases (MAMER). Four of the centers had more than 1000 patients, and 12 had less than 100 (see Table 1). Data from all of the centers, except one, belonged to patients operated in or after year 2005. All of the cases from Ege University were entered in year 2005, representing a retrospective recording of patients treated over the past 14 years. The number of patients with data who had been operated before that date was 3,942.

1 Gender

The number of patients included in the gender database was 11,504, including 11,385 (99%) female and 119 (1%) male patients. Data on breast cancers diagnosed in male patients will be reported in a future supplement to this report.

The data shows a breast cancer patient profile of 99% female and 1% male in Turkey, similar to global examples.

2 Age

The number of female patients included in the age database diagnosed with breast cancer was 11,385 (100.0%) (see Table 2).

Age at diagnosis	n	%
<15	5	0.0
15 – 19	11	0.1
20 – 24	51	0.4
25 – 29	190	1.7
30 – 34	597	5.2
35 – 39	1,096	9.6
40 – 44	1,583	13.9
45 – 49	1,900	16.7
50 – 54	1,583	13.9
55 – 59	1,318	11.6
60 – 64	1,042	9.2
65 – 69	860	7.6
70+	1,149	10.1
Total	11,385	100.0

Table 2.Women diagnosed with breast cancer by age at diagnosis.

In this group, the mean age at diagnosis was 51.6 (±12.6; range 12 – 97), and median age was 50 (range 12 – 97). Relationship between breast cancer patients and age groups, and the distribution of cases by age group are illustrated in Figure 10 and Figure 11, respectively.

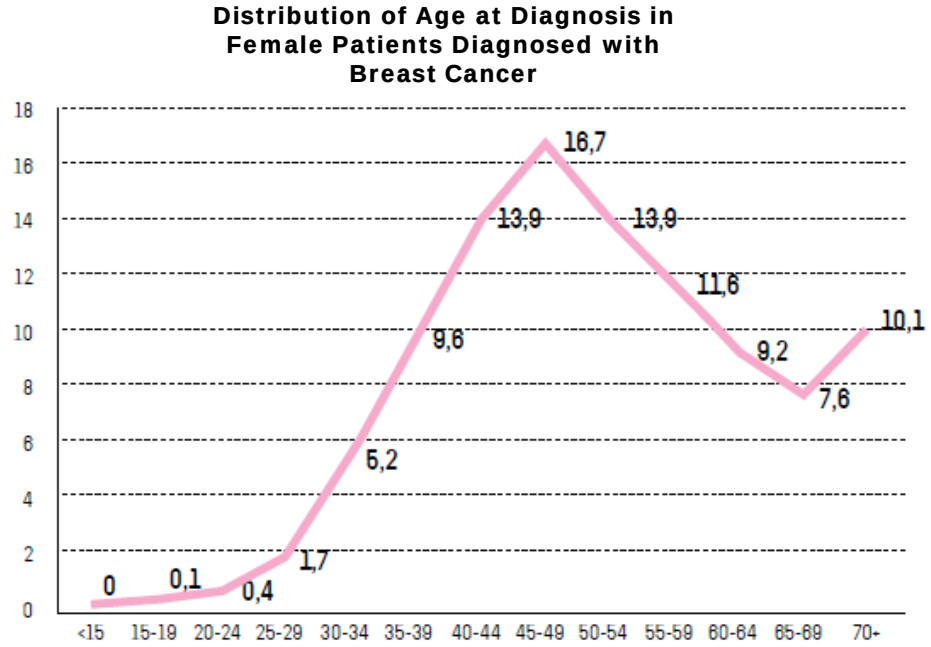


Figure 10. Incidence of breast cancer by age at diagnosis (%)

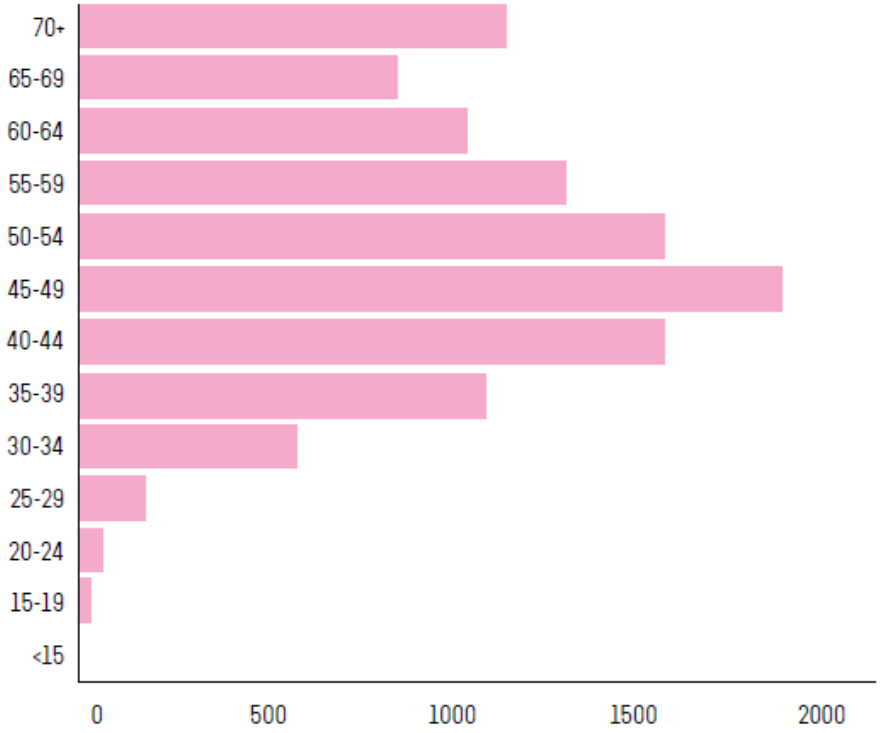


Figure 11.Prevalence of breast cancer by age at diagnosis

As illustrated in Table 2, 3,483 patients in the 40 – 49 age group (30.6%) were diagnosed with and treated for breast cancer. The number of women with breast cancer aged 49 or younger were 5,433 (48%), and those aged ≥50 were 5,952 (52%), ≥ 70 1,149 (10%), and ≤40 1,950 (17%) (see Table 3).

Age at diagnosis	n	%
<40	1,950	17.1
≥40	9,435	82.9
Total	11,385	100.0

Table 3.Women diagnosed with breast cancer by age at diagnosis (<40 vs. ≥40).

Looking at the graphics by age group (Figures 10 and 11), we see that incidence of breast cancer rose rapidly up to the age of 50, peaking between years 45 and 49 (17%), and then declined to 7.6% between years 65 and 69, to rise again to 10% after the age of 70.

3 Menopausal status

The number of patients with menopausal status data were 5,471 (48%). 2,440 of these (45%) were premenopausal women, and 3,031 (55%) menopausal. The relationship between patients' menopausal status and clinical stage at diagnosis, pathological tumor diameter, pathological stage, estrogen and progesterone receptor expression of tumor cells, HER 2 receptor expression, and molecular subtypes of tumors was studied.

4 Histopathological type

The number of patients included in the histopathological tumor type database was 4,510 (39.6%), of whom 223 (5%) had ductal carcinoma in situ (DCIS), 3,376 (75%) had invasive ductal cancer (IDC), 317 (7%) had invasive lobular cancer (ILC), and 412 (9%) had invasive mixed cancer (IMC). Other histopathological types (inflammatory carcinoma, tubular, intracystic papillary carcinoma, etc.) were observed in 173 (4%) of the patients (see Table 4). Considering only invasive breast cancers, the total number of patients was 4,287 (95% of all patients), of whom 79% had invasive ductal cancers, 7.4% had invasive lobular cancers (ILC), 9.8% had mixed type cancers (ILC + IDC), and the remaining 3.8% had other histopathological types.

Histological diagnosis	Number (n)	%
Ductal Carcinoma in situ (DCIS)	223	4.9
Invasive Breast Cancer	4,287	95.1
Total	4,510	100.0

Table 4A.Invasive and in situ cancer incidence in breast cancer patients.

Patients were categorized in two groups by age, i.e. ≥40 and <40, and in three groups by histopathological type, i.e. invasive ductal, invasive lobular and mixed to examine any relationships between them (see Table 5). 18.5% of patients with a known histological type were aged below 40, and 81.5% were 40 years of age or older. 19% of patients diagnosed with IDC were <40, and 81% ≥40; the percentages in patients with ILC+IMC were 15% and 85%, respectively. In the younger group (<40 years), the percentage of IDC were statistically higher than that of other histological types (p=0.017).

Age at diagnosis	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
40	645	19	113	15	758	18.5
≥40	2726	81	623	85	3349	81.5
Total	3371	100	736	100	4107	100.0

Table 5.Histopathological types in women diagnosed with invasive breast cancer, sortedby 40 years of age

The cases were categorized in two groups based on menopausal status (premenopausal vs. menopausal) and tumor histopathological type (invasive ductal vs. invasive lobular vs. mixed), and the relationship between the two groups was examined (see Table 6). Histopathological tumor types were at similar levels in premenopausal and menopausal patients (p>0.05).

Menopausal status	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
Premenopausal	1469	46.3	314	45	1783	46
Menopausal	1704	53.7	384	55	2088	54
Total	3173	100.0	698	100.0	3871	100.0

Table 6. Relationship between menopausal status and tumor histopathological type in women diagnosed with invasive breast cancer.

Patients classified in two groups of those with pathological lymph node involvement (pN1-3) and those without it (pN0) were further grouped by tumor histopathological type, i.e. invasive ductal vs. invasive lobular + mixed. The percentage of pN0 (49.8%) and pN1-3 (50%) were very close in all patients. Axillary involvement rates were compared between different histological groups (see Table 7). 52% of patients with IDC were pN0, compared to 41% of patients with ILC and IMC, representing significantly higher axillary involvement in patients with ILC and IMC compared to those with IDC (p=0.0001).

	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
pN0	1109	51.7	189	40.8	1298	49.8
pN1-3	1034	48.3	274	59.2	1308	50.2
Total	2143	100.0	463	100.0	2606	100.0

Table 7. Relationship between regional lymphatic involvement and tumor histopathological type in women diagnosed with invasive breast cancer.

Tumors were divided into two groups of HG I-II and III, based on histological grade (HG), and their relationship with histological types (IDC and ILC+IMC) was examined (see Table 8). The detection rates of low, medium and high grade tumors were comparable for both histopathological types, without a statistically significant difference between groups.

Histological Grade	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
I, II	1310	49.8	267	49.4	1577	49.8
III	1318	50.1	273	50.6	1591	50.2
Total	2628	100.0	540	17.0	3168	100.0

Table 8. Relationship between histological grade and histopathological type in women diagnosed with invasive breast cancer.

75% of women with invasive breast cancer had early (Stage I-II) and 25% had locally advanced or metastatic (Stage III-IV) breast cancer. Patients at these two stage groups were compared based on tumor histopathological type (see Table 9). 76.5% of patients had early stage IDC, and 68.5% had early stage IDC+IMC.

Pathological Stage	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
Early (I, II)	1636	76.5	315	68.2	1951	75.0
Locally advanced / metastatic (III, IV)	503	23.5	147	31.8	650	25.0
Total	2139	100.0	462	100.0	2601	100.0

Table 9. Relationship betweenpathological stage and histopathological type in women diagnosed with invasive breast cancer.

It was statistically significant that more patients with ILK and IMC tumors were at the advanced stage compared to patients with IDC (p=0.0001).

Patients were divided into two groups based on tumor diameter, T1-T2 (≤5 cm) and T3 (>5 cm), and histopathological types of tumors detected in these patients were further divided to two groups of invasive ductal and invasive lobular + mixed, and the relationships between these groups were examined (see Table 10). Patients' overall pT1-2 rate was 94%, and pT3 rate was 6%. Tumor diameters were ≤5 cm (pT1-2) in 95% of patients with IDC, and >5 cm (pT3) in 5%.

Pathological tumor diameter	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
T1, T2 (≤5.0 cm)	2883	94.6	613	91.8	3496	94.0
T3 (>5.0 cm)	166	5.4	55	8.2	221	6.0
Total	3049	100.0	668	18.0	3717	100.0

Table 10. Relationship between pathological diameter and histopathological type in women diagnosed with invasive breast cancer.

These percentages were 92% and 8%, respectively, in the other histological group (ILC+IMC) (p=0.006).

Percentage of HER-2 positive patients among those with a known histological type was 23% (see Table 11). HER-2 expression was 24.5% in patients with IDC, and 14% in those with ILC+IMC, representing a statistically significant difference (p=0.0001, see Table 11).

HER-2 Expression	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
Positive	336	24.5	40	14.0	376	22.7
Negative	1037	75.5	247	86.0	1284	77.3
Total	1373	100.0	287	100.0	1660	100.0

Table 11. Relationship betweenHER-2 expression and histopathological type in women diagnosed with invasive breast cancer.

Histopathological types of tumors detected in patients were divided into two groups of invasive ductal and invasive lobular plus mixed, and patients were compared to those with estrogen receptor (ER) positive or negative tumor cells. The percentage of ER positive patients were 70% overall, 68% in patients with IDC, and 78% in patients with ILC+IMC (p=0.0001, see Table 12).

ER Expression	Invasive ductal cancers		Invasive lobular and mixed cancers		Total	
	n	%	n	%	n	%
Positive	1887	68.0	466	78.0	2353	70.0
Negative	882	32.0	131	22.0	1013	30.0
Total	2769	100.0	597	17.7	3366	100.0

Table 12. Relationship between estrogen receptor (ER) expression and histopathological type in women diagnosed with invasive breast cancer.

5 Clinical Stage

Clinical stage distribution of patients with clinical stage data available in the database were as follows (see Table 13): Stage 0 (DCIS) 3% (197 cases), Stage 1 26% (1,453 cases), Stage II 54% (2,971 cases), Stage III 14% (839 cases), and Stage IV 3% (188 cases). In all age groups, the highest number of cases (82%) were at the early stage (stage 0-II). In this group, stage II was the most common clinical stage, followed by stage I. Percentage of stage III breast cancersamong female patients below the age of 40 was 19%, and 12.7% in the age group 60 – 69. The incidence of stage III disease declined by age, but rose back again at 70 years and above.

Looking at clinical stages based on age group, percentage of early stage breast cancers (stage 0-II) was 78%, and stage III and IV breast cancers 22% in women aged ≤40 years (see Table 13). Incidence of early stage breast cancer increased significantly (p=0.001) by age. Percentage of stage I breast cancers was 21% in women aged ≤40 years, and 29% in the age group 50 – 59 (p<0.05). Number of patients diagnosed at clinical stage I rose, and those diagnosed at the advanced stage declined by age, particularly between 40 and 60 years (see Figure 12). The percentage of stage IV disease was similar across all age groups (see Figure 13), without a statistically significant difference between them.

Age at diagnosis	Clinical Stage										Total	
	Stage 0 (DCIS)		Stage I		Stage II		Stage III		Stage IV			
	n	%	n	%	n	%	n	%	n	%	n	%
40	30	3.0	210	21.0	538	53.7	190	19.0	33	3.3	1001	17.7
40 – 49	61	3.6	430	25.0	922	53.7	245	14.3	59	3.4	1717	30.4
50 – 59	59	4.2	405	29.0	698	50.0	189	13.5	44	3.2	1395	24.7
60 – 69	32	3.5	250	27.1	494	53.5	117	12.7	30	3.3	923	16.3
≥70	15	2.5	158	25.8	319	52.1	98	16.0	22	3.6	612	10.8
Total	197	3.5	1453	25.7	1971	52.6	839	14.9	188	3.3	5648	100.0

Table 13. Relationship betweenage at diagnosis and clinical stage in women diagnosed with invasive breast cancer.

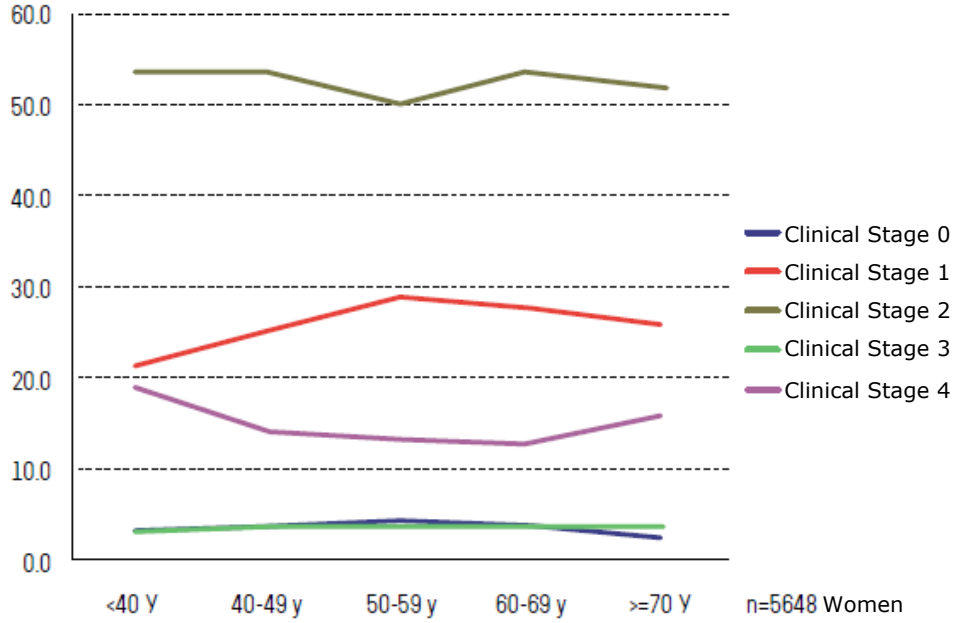


Figure 12.Relationship between age at diagnosis and clinical stage in breast cancer patients.

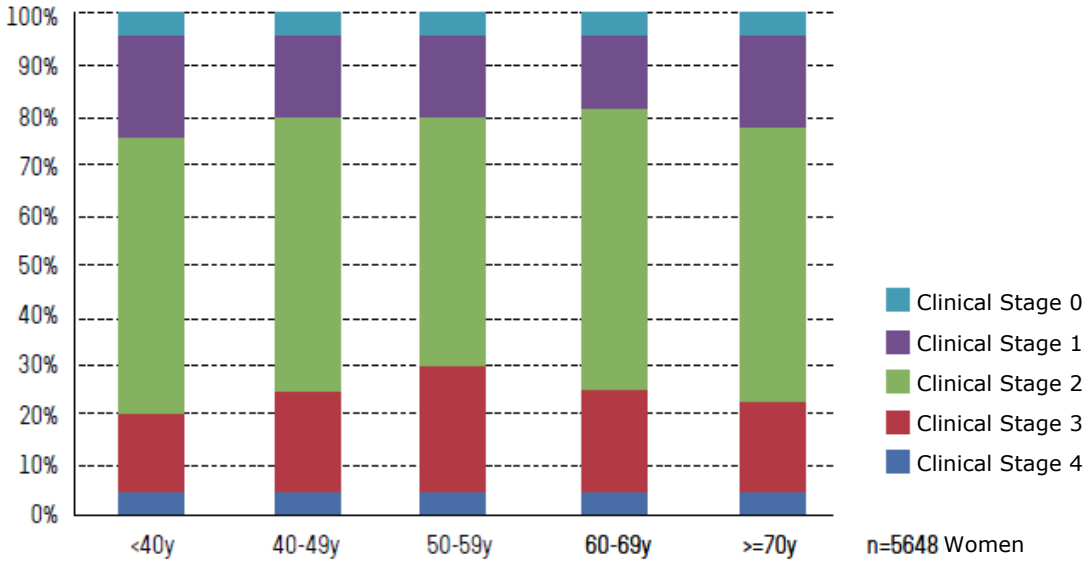


Figure 13.Distribution of clinical stageby age at diagnosis in breast cancer patients.

The relationship between menopausal status and clinical stage at diagnosis was examined in invasive breast cancer patients with data on their menopausal status and clinical stage available in the database (see Table 14). Percentage of early stage breast cancers were lower in premenopausal patients compared to menopausal ones, but the difference was not statistically significant (p>0.05).

Menopausal status	Clinical Stage										Total	
	Stage 0		Stage I		Stage II		Stage III		Stage IV			
	n	%	n	%	n	%	n	%	n	%	n	%
Premenopausal	88	3.6	599	24.5	1304	53.4	390	16.0	59	2.4	2440	44.6
Postmenopausal	109	3.6	823	27.2	1561	51.5	412	13.6	126	4.2	3031	55.4
Total	197	3.6	1422	26.0	2865	52.4	802	14.7	185	3.4	5471	100.0

Figure 14.Relationship between menopausal status and clinical stage at diagnosis in women with invasive breast cancer.

6 Pathological Tumor Diameter

The mean tumor diameter was 2.5 cm (±1.6 cm; range 0.1 – 20 cm), and median tumor diameter was 2.2 cm in all age groups (see Table 15).

Age at Diagnosis	Tumor Diameter (cm)	
	Mean	Median
<40	2.8	2.5
40 – 49	2.5	2.1
50 – 59	2.4	2.0
60 – 69	2.4	2.0
≥70	2.8	2.5
Total	2.5	2.2

Table 15. Mean and median pathological tumor diameters, and their relationship with age group in women with invasive breast cancer.

The relationship between age and the tumor diameter measured according to AJCC (American Joint Committee on Cancer) criteria (33) (see Table 16). 48% of women diagnosed with invasive breast cancer had T1 tumors (≤2 cm), 46% had T2 tumors (2 – 5 cm), and 6% had T3 tumors (>5 cm). Particularly in patients aged between 40 and 60 years, tumor sizes observed were smaller with increased age, but this difference was not statistically significant. Further, this tumor size reduction trend slows between 60 and 69 years, and then increase again in women aged >70 years to the level of women aged <40 years.

Age at diagnosis	Tumor diameter (cm)						Total	
	T1 (≤2.0)		T2 (2.1 – 5.0)		T3 (>5.0)			
	n	%	n	%	n	%	n	%
<40	294	42.6	336	48.7	60	8.7	690	100.0
40 – 49	578	49.6	511	43.8	77	6.6	1166	100.0
50 – 59	465	50.4	415	45.0	42	4.6	922	100.0
60 – 69	308	50.2	281	45.8	24	3.9	613	100.0
≥70	180	43.0	207	49.4	32	7.6	419	100.0
Total	1825	47.9	1750	45.9	235	6.2	3810	100.0

Table 16.Relationship between age at diagnosis and pathological tumor diameter in patients diagnosed with invasive breast cancer.

Patients were divided in two age groups of ≥40 and <40, and the distribution of pathological tumor sizes was examined in each group (see Table 17). The percentage of T1 tumors was 43% in women aged less than 40 years, and 50% in women aged ≥30, representing a statistically significant difference (p=0.0001). Also, the percentage of women with T2 and T3 tumors were significantly higher in the <40 years age group (p=0.0001). Findings in women in the age groups <40 and ≥40 were further analyzed; the odds ratio (OR) was 1.4, meaning that the likelihood of tumor diameter measured at diagnosisto be ≤2 cm was 1.4-fold higher in women aged ≥40, than in women aged <40.

Tumor diameter	Age at diagnosis				Total	
	<40		≥40			
	n	%	n	%	n	%
T1 (≤2.0 cm)	302	42.7	1606	49.6	1908	48.4
T2 (2.1 – 5.0 cm)	343	48.4	1448	44.7	1791	45.4
T3 (>5.0 cm)	63	8.9	184	5.7	247	6.3
Total	708	100.0	3238	100.0	3946	100.0

Table 17.Relationship between pathological tumor diameter and age group.

The relationship between patients' menopausal status and pathological tumor diameters was examined (see Table 18). 47% of premenopausal women, and 49% of postmenopausal women had pT1 (p=0.059).

Menopausal status	Tumor diameter (cm)						Total	
	T1 (≤2.0)		T2 (2.1 – 5.0)		T3 (>5.0)			
	n	%	n	%	n	%	n	%
Premenopausal	810	47.3	780	45.6	121	7.1	1711	100.0
Postmenopausal	962	49.0	900	45.8	102	5.2	1964	100.0
Total	1772	48.2	1680	45.7	223	6.1	3675	100.0

Table 18.Relationship between menopausal status and pathological tumor diameter in patients with invasive breast cancer.

7 Pathological Lymphatic Stage

Lymph node involvement in patients diagnosed with invasive breast cancer, whose pathological lymphatic stage data were available in the database, were as follows (see Table 19): pN0 50%, pN1 28%, pN2 15%, and pN3 7%. Looking at the relationship between lymph node involvement and age group, we found that 44% of women aged <40 diagnosed with invasive cancer, and 55% of women aged between 60 and 69 years were pN0 (see Figure 14).

Age at diagnosis	Pathological Lymphatic Stage								Total	
	N0		N1		N2		N3			
	n	%	n	%	n	%	n	%	n	%
<40	199	43.6	142	31.1	82	18.0	33	7.2	456	100.0
40 – 49	399	47.7	240	28.7	129	15.4	68	8.1	836	100.0
50 – 59	345	52.0	175	26.4	95	14.3	48	7.2	663	100.0
60 – 69	227	54.6	118	28.4	53	12.7	18	4.3	416	100.0
≥70	165	55.6	70	23.6	41	13.8	21	7.1	297	100.0
Total	1335	50.0	745	27.9	400	15.0	188	7.0	2668	100.0

Table 19.Distribution of pathological regional lymphatic stages by age at diagnosis in patients with invasive breast cancer.

Patients without pathological lymph node involvement (pN0) were mostly in the ≥70 age group. It was noted that regional lymphatic involvement declined by age at diagnosis, and hence the lymphatic stages were lower. In other words, the number of pN1 and pN2 patients declined, and the number of pN0 patients rose with higher age at diagnosis. These findings were statistically significant (p=0.0001). However, a similar relationship was not found in pN3 patients.

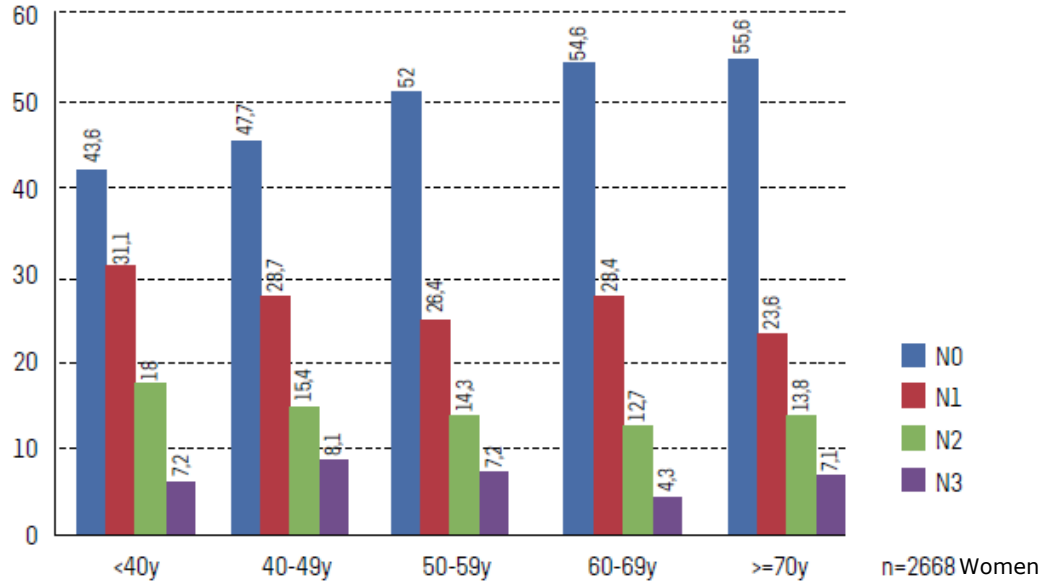


Figure 14.Distribution of tumor pathological regional lymphatic stage by age at diagnosis in patients with invasive breast cancer.

Patients were divided into two age groups of ≥40 and <40, and pathological lymph node involvement was examined in each group (see Table 20). 44% of women diagnosed with invasive cancer aged below 40 years, and 51% of women aged ≥40 were pN0. In the below-40 group, the prevalence of pN1 and pN2 involvement was higher than the other group. However, pN3 involvement was similar in both groups. The difference between pN0 and pN1-N2 lymphatic involvement in the two age groups was statistically significant (p=0.001). Patients were grouped based on age (≥40 and <40) and whether they had (pN1-3) or had not (pN0) pathological lymph node involvement (see Figure 15), and relationships between the groups were examined (see Table 20). Ratio of pN1-3 patients to pN0 patients in the <40 group was 1.29, compared to 0.94 in the ≥40 group. The odds ratio for detecting lymphatic involvement in the two groups was 1.37. In other words, the likelihood of detecting lymphatic involvement was 1.4-fold higher in the <40 group, than the ≥40 group.

Regional Lymph node Status	Age at diagnosis				Total	
	<40		≥40			
	n	%	n	%	n	%
N0	199	43.6	1136	51.4	1335	50.0
N1	142	31.1	603	27.3	745	27.9
N2	82	18.0	318	14.4	400	15.0
N3	33	7.2	155	7.0	188	7.0
Total	456	100.0	2212	100.0	2668	100.0

Table 20.Relationship between regional lymphatic involvement and age group.

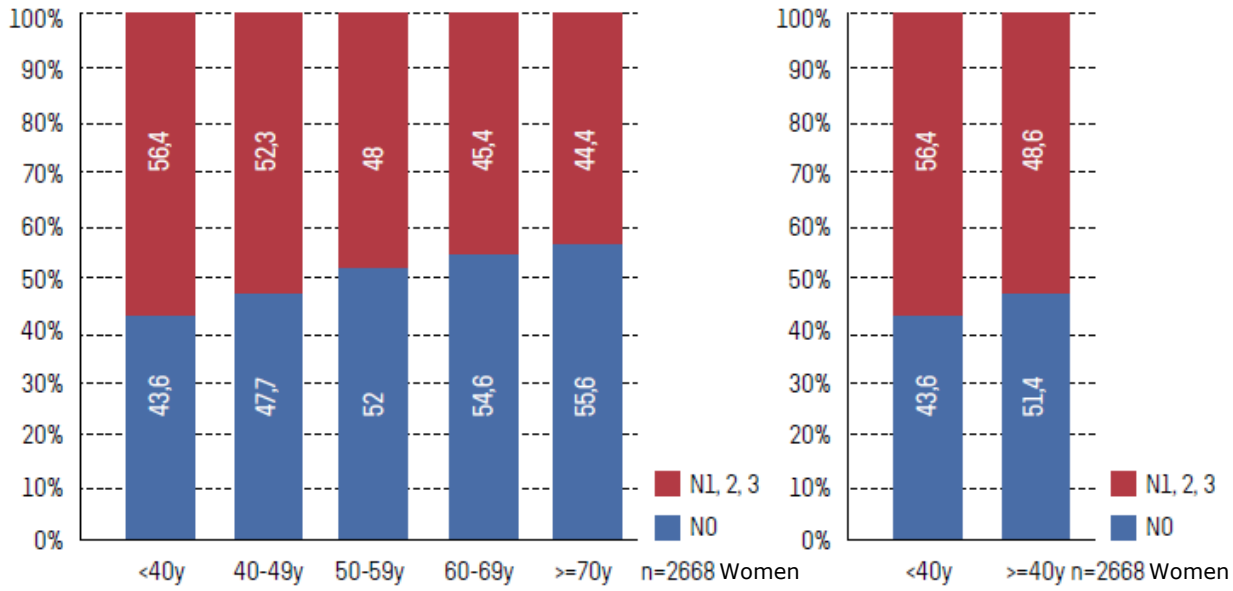


Figure 15. Relationship between age at diagnosis and lymphatic involvement in patients diagnosed with breast cancer.

Pathological lymphatic involvement level of patients was examined based on menopausal status (see Table 21). 47% of premenopausal women and 53% of menopausal women were pN0. Similarly, pathological lymphatic involvement was higher in premenopausal women with breast cancer than menopausal ones at all of the N1, N2 and N3 levels. The differences detected were statistically significant in all cases (p=0.018).

Menopausal status	Pathological Lymphatic Stage								Total	
	N0		N1		N2		N3			
	n	%	n	%	n	%	n	%	n	%
Premenopausal	598	47.0	377	29.6	205	16.1	92	7.2	1272	100.0
Postmenopausal	737	52.8	368	26.4	195	14.0	96	6.9	1396	100.0
Total	1335	50.0	745	27.9	400	15.0	188	7.0	2668	100.0

Table 21.Distribution of pathological lymphatic stage by menopausal status in patients with invasive breast cancer.

Patients were divided into groups of premenopausal and postmenopausal ones, and those with (pN1-3) or without (pN0) pathological lymph node involvement, and relationships between the groups were examined (see Table 22). Absence of lymphatic involvement at any level in menopausal patients was 53%, representing a statistically significant difference (p=0.003)

	Menopausal status				Total	
	Premenopausal		Postmenopausal			
	n	%	n	%	n	%
N0	598	47.0	737	52.8	1335	50.0
N1+N2+N3	674	53.0	659	47.2	1333	50.0
Total	1272	100.0	1396	100.0	2668	100.0

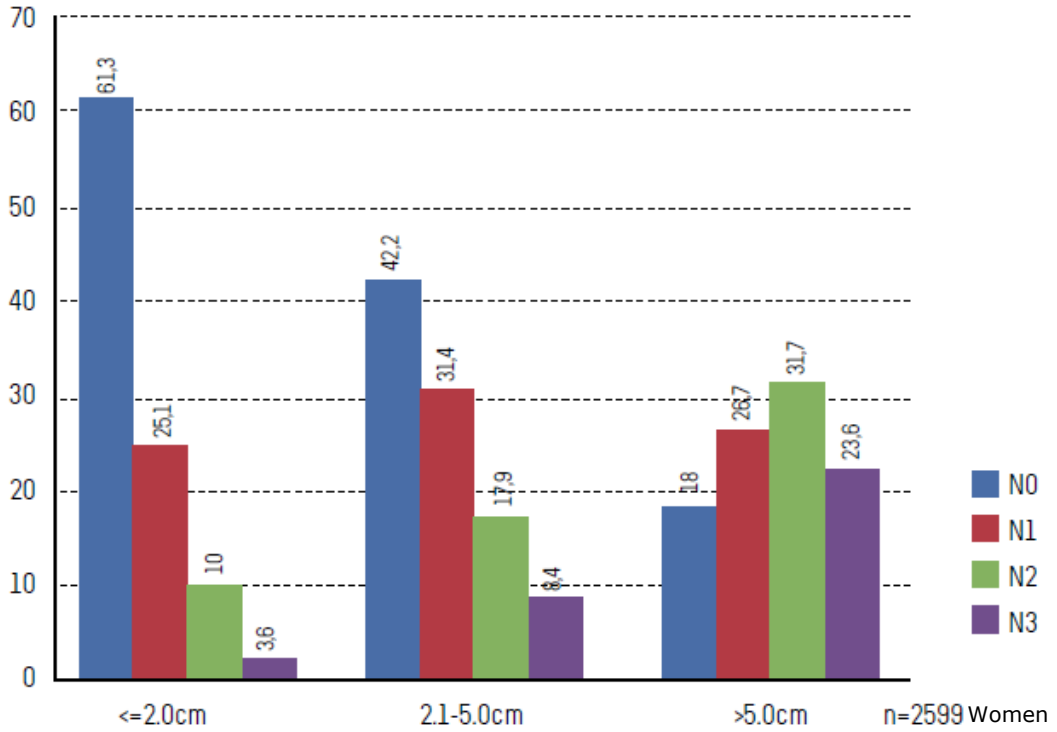
Table 22. Relationship between menopausal status and pathological lymphatic involvement in patients diagnosed with invasive breast cancer.

The ratio of premenopausal patients with lymphatic involvement to patients to those without lymphatic involvement was 1.12, and that of pN1-3 menopausal patients to pN0 ones was 0.9. The odds ratio for having lymphatic involvement for patients in these two menopausal groups was 1.24. In other words, the likelihood of detecting lymphatic involvement was 1.24-fold higher in premenopausal patients, than postmenopausal ones.

Relationshipswere examined between patients diagnosed with invasive breast cancer, whose pathological tumor diameter data and regional lymphatic stage data were available in the database (see Table 23). 61% of patients with 2 cm or smaller-diameter invasive tumors (pT1) were pN0, compared to 42% and 18% in patients with pT2 and pT3 tumors, respectively (see Figure 16). Similarly, the number of patients with lymphatic stage pN1-3 grew in parallel with the increasing tumor diameter. The increase in regional lymphatic involvement paralleling tumor diameter increase was statistically significant (p=0.0001).

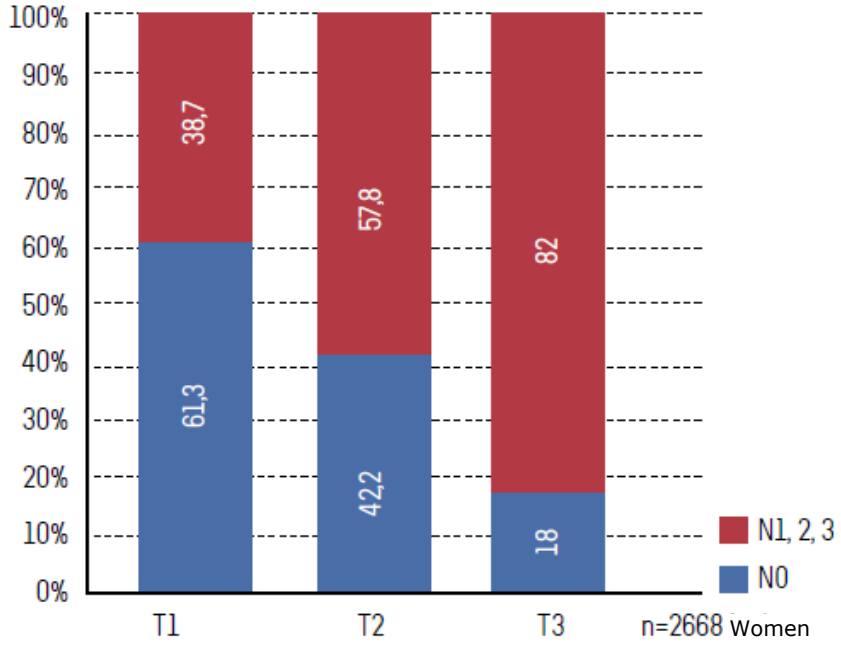
Tumor diameter (cm)	Pathological Lymphatic Stage								Total	
	N0		N1		N2		N3			
	n	%	n	%	n	%	n	%	n	%
T1 (≤2.0)	779	61.3	319	25.1	127	10.0	46	3.6	1271	100.0
T2 (2.1 – 5.0)	493	42.2	367	31.4	209	17.9	98	8.4	1167	100.0
T3 (>5.0)	29	18.0	43	26.7	51	31.7	38	23.6	161	100.0
Total	1301	50.1	729	28.0	387	14.9	182	7.0	2599	100.0

Table 23.Relationship between pathological tumor diameter and pathological lymphatic stage in patients with invasive breast cancer.



Graphic 16.Relationship between pathological tumor diameter and pathological lymphatic stage in patients with invasive breast cancer.

Patients were divided into three groups based on tumor diameter (pT1,2,3), and into two groups based on pathological lymph node involvement, and the relationship between these groups was examined (see Figure 17 and Table 24). The percentage of pT1 patients without any degree of lymphatic involvement (pN0) was 61%, which was statistically lower than those with lymphatic involvement (p=0.0001). By contrast, the percentage of lymphatic involvements was higher in pT2-3 tumors (p=0.0001). The ratio of patients with pT1 and lymphatic involvement to those without lymphatic involvement was 0.63, compared to 1.36 and 4.55 in patients with pT2 and pT3, respectively. The odds ratio of lymphatic involvement was 2.15 between groups with pT2 and pT1; the odds ratio of lymphatic involvement between groups pT3 and pT1 was, however, higher (OR=7.2). In other words, the likelihood of detecting lymphatic involvement in patients with pT2 or pT3 tumors was 2.15- and 7.2-fold higher, respectively, than the likelihood of detecting lymphatic involvement in patients with pT1 tumors.



Graphic 17. Relationship between pathological tumor diameter and regional lymphatic involvement at diagnosis in patients diagnosed with breast cancer.

Tumor diameter (cm)	Pathological Lymphatic Stage				Total	
	N0		N1-3			
	n	%	n	%	n	%
T1 (≤2.0)	779	61.3	492	38.7	1271	100.0
T2 (2.0 – 5.0)	493	42.2	674	57.8	1167	100.0
T3 (>5.0)	29	18.0	132	82.0	161	100.0
Total	1301	50.1	1298	49.9	2599	100.0

Table 24.Relationship between pathological tumor diameter and pathological lymphatic involvement in patients with invasive breast cancer.

8 Pathological Stage

Distribution of stages was as follows for patients, whose pathological stage data were available in the database (see Table 25): Stage 0 4.9%, Stage I 27%, Stage II 45%, Stage III 21%, and Stage IV 3%. Looking at the relationship between pathological stage and age group, we found that pathological stage decreased withincreasing age, which was statistically significant (p=0.011). However, the relationship between increasing age and pathological stage was less manifest in the 60 – 69 age group, and minimal in patients aged more than 70 years.

Pathological Lymphatic Stage												
Age at diagnosis	Stage 0		Stage I		Stage II		Stage III		Stage IV		Total	
	n	%	n	%	N	%	n	%	n	%	n	%
<40	23	3.6	140	22.2	285	45.1	163	25.8	21	3.3	632	100.0
40 – 49	60	5.1	295	25.0	550	46.6	243	20.6	32	2.7	1180	100.0
50 – 59	57	6.0	286	29.9	414	43.3	179	18.7	21	2.7	957	100.0
60 – 69	26	4.3	175	29.1	269	44.8	115	19.1	16	2.7	601	100.0
≥70	18	4.4	111	27.1	178	43.4	87	21.2	16	3.9	410	100.0
Total	184	4.9	1007	26.6	1696	44.9	787	20.8	106	2.8	3780	100.0

Table 25.Relationship between age at diagnosis and pathological stage in patients with breast cancer.

To more closely examine the relationship between age group and pathological stage, patients were divided into two age groups of ≥40 and <40, and the distribution of pathological stages across these groups was examined (see Table 26). The percentage of cases detected at early stage (Stage 0,I,II) was 71.5%, and those detected in advanced stage (Stage III,IV) was 28.5% in women aged less than 40 years. In patients aged 40 years or older, however, the percentage of cases detected at early versus advanced stage was 77.5% and 22.5%, respectively. Consistent with the findings illustrated in Table 13, the frequency of advanced stage (stage II, IV) disease was higher among patients younger than 40 years, which was statistically significant (p=0.005). The likelihood of early stage breast cancer in the ≥40 age group was 1.37-fold higher than in the <40 age group (1832 / 531 vs. 342 / 136).

Pathological Stage	Age at diagnosis				Total	
	<40 y		≥40 y			
	n	%	n	%	n	%
Early Stage (Stage 0, I, II)	342	71.5	1832	77.5	2174	76.5
Advanced Stage (Stage III, IV)	136	28.5	531	22.5	667	23.5
Total	478	100.0	2363	100.0	2841	100.0

Table 26.Relationship between patients' pathological stage and age group.

Looking at the relationship between patients' pathological stage and menopausal status (see Table 27), we found that 75.5% of premenopausal women and 77% of postmenopausal women were diagnosed with early stage breast cancer (stage I, II), and the pathological stage difference between these two groups was not statistically significant.

Menopausal status	Pathological Stage											
	Stage 0		Stage I		Stage II		Stage III		Stage IV		Total	
	n	%	n	%	N	%	n	%	n	%	n	%
Premenopausal	81	4.8	423	25.0	776	45.8	376	22.2	39	2.3	1695	100.0
Postmenopausal	103	4.9	583	28.0	919	44.2	410	19.7	66	3.2	2081	100.0
Total	184	4.9	1006	26.6	1695	44.9	786	20.8	105	2.8	2776	100.0

Table 27.Relationship between menopausal status and pathological stage in women with breast cancer.

9 Histological Grade (HG)

Distribution of histological grades of patients registered in the database was as follows: HG I 5%, HG II 45%, and HG III 50% (see Table 28). Half of the patients had HG III tumors, and HG decreased withincreasing age at diagnosis (p=0.0001).

Age at diagnosis	Histological Grade						Total	
	I		II		III			
	n	%	n	%	n	%	n	%
<40	16	2.6	230	37.5	367	59.9	613	100.0
40 – 49	53	5.5	416	43.2	494	51.3	963	100.0
50 – 59	36	4.6	371	47.7	371	47.7	778	100.0
60 – 69	29	5.5	267	50.9	229	43.6	525	100.0
≥70	13	3.9	162	48.6	158	47.4	333	100.0
Total	147	4.6	1446	45.0	1619	50.4	3212	100.0

Table 28.Distribution of tumor histological grade by age at diagnosis in patients with invasive breast cancer.

To more closely examine the relationship between age group and histological grade, patients were divided into two age groups of ≥40 and <40, and the distribution of histological grades across these groups was examined (see Table 29). 60% of tumors detected in patients aged less than 40 years, and 48% of those in patients aged ≥40 years were HG III, representing a statistically significant difference (p=0.0001). The ratio of HG III tumors to tumors of other grades (I and II) was 1.49 in patients younger than 40 years, and 0.92 in patients aged ≥40 years (1252 / 1347). The odds ratio for detecting HG III tumors in patients aged <40 vs. ≥40 was 1.6 (OR=1.49/0.92); the odds ratio for detecting grade I tumors in patients aged <40 vs. ≥40 was 2.5. In other words, the likelihood of detecting HG III tumors was 1.6-fold higher in patients aged<40 years, than in patients aged ≥40 years.

Histological Grade	Age at diagnosis				Total	
	<40 y		≥40 y			
	n	%	n	%	n	%
Grade I	16	2.6	131	5.0	147	4.6
Grade II	230	37.5	1216	46.8	1446	45.0
Grade III	367	59.9	1252	48.2	1619	50.4
Total	613	100.0	2599	100.0	3212	100.0

Table 29.Relationship between age group and the histological grade of tumors detected in patients.

The relationship between pathological tumor diameter and histological grade was examined in patients with invasive breast cancer, whose pathological tumor diameter data and histological grade data were available in the database (see Table 30). Only 44.5% of patients with tumor diameter ≤2 cm (pT1) were HG III, although it rose with increasing tumor diameter to 57% with pT2, and to 61% with pT3. Consistent with this finding, the percentage of grade I and II tumors declined with increasing tumor diameter. The difference between the groups was statistically significant (p=0.0001).

Tumor diameter (cm)	Histological Grade						Total	
	I		II		III			
	n	%	n	%	n	%	n	%
T1 (<2.0)	111	7.8	678	47.7	632	44.5	1421	100.0
T2 (2.0 – 5.0)	22	1.6	582	41.7	792	56.7	1396	100.0
T3 (>5.0)	4	2.5	57	36.1	97	61.4	158	100.0
Total	137	4.6	1317	44.3	1521	51.1	1975	100.0

Table 30.Relationship between tumor diameter and histological grade in patients with invasive breast cancer.

The relationship between pathological lymphatic stage and histological grade was examined in patients with invasive breast cancer, for whom data on these two parameters were available in the database (see Table 31). 51% of patients without regional lymphatic involvement (pN0) were HG III. However, the HG III percentage rose significantly with increasing lymphatic involvement. 71% of patients with ≥10 axillary lymph node involvement (pN3) were HG III. In contrast to this finding, percentage of HG I and II tumors decreased with increasing regional lymphatic stage. Statistically, differences in both directions were significant (p=0.0001).

Pathological Lymphatic Stage	Histological Grade						Total	
	I		II		III			
	n	%	n	%	n	%	n	%
N0	60	6.2	414	42.5	499	51.3	973	100.0
N1	21	3.7	231	40.9	313	55.4	565	100.0
N2	3	1.0	113	38.7	176	60.3	292	100.0
N3	2	1.4	39	27.7	100	70.9	141	100.0
Total	86	4.4	797	40.4	1088	55.2	1971	100.0

Table 31.Distribution of histological grade by regional pathological lymphatic stage.

Patients were divided into three groups based on histological grade (HG I, II, and III) and into two groups based on pathological lymph node involvement (pN- and pN+), and the relationship between these groups was examined (see Table 32). Only 30% of HG I patients had lymphatic involvement (pN+). Lymphatic involvement rate increased significantly (p=0.0001) with increasing HG. 48% of invasive breast cancer patients whose HG was II, and 59% of those whoseHG was III were axillary positive (pN+).

Pathological Lymphatic Stage	Histological Grade						Total	
	I		II		III			
	n	%	n	%	n	%	n	%
N0	60	6.2	414	42.5	499	51.0	973	100.0
N1-3	26	2.6	383	48.0	589	59.0	998	100.0
Total	86	4.4	797	40.4	1088	55.2	1971	100.0

Table 32.Relationship between tumor histological grade and pathological regional lymphatic involvement in patients diagnosed with invasive breast cancer.

10 Hormone Receptor Expression

A) Estrogen Receptor (ER) Expression

69% of patients, whose estrogen receptor expression data were available in the database, were estrogen receptor (ER) positive (see Table 33). Patients were divided into two age groups of ≥40 years and <40 years, and evaluated for ER expression (see Table 33). 61% of patients aged <40 years, and 71% of those aged ≥40 were ER positive, representing a statistically significant difference between the two groups (p=0.0001).

Estrogen Receptor	Age at diagnosis				Total	
	<40 y		≥40 y			
	n	%	n	%	n	%
Positive	379	60.8	2004	71.1	2383	69.2
Negative	244	39.2	815	28.9	1059	30.8
Total	623	100.0	2819	100.0	3442	100.0

Table 33.Estrogen receptor (ER) expression by age at diagnosis in patients with invasive breast cancer.

ER expression of patients, whose estrogen receptor expression data and menopausal status data were available in the database, was examined based on menopausal status (see Table 34). 66% of premenopausal patients, and 73% of menopausal patients were ER positive, representing a statistically significant difference between the two groups (p=0.0001).

Estrogen Receptor	Menopausal status				Total	
	Premenopausal		Postmenopausal			
	n	%	n	%	n	%
Positive	1020	66.1	1299	72.8	2319	69.7
Negative	524	33.9	485	27.2	1009	30.3
Total	1544	100.0	1784	100.0	3328	100.0

Table 34.Relationship between patient menopausal status and estrogen receptor (ER) expression.

B) Progesterone Receptor (PR) Expression

58% of patients, whose progesterone receptor expression data were available in the database, were progesterone receptor (PR) positive (see Table 35).

Progesterone Receptor	Age at diagnosis				Total	
	<40 y		≥40 y			
	n	%	n	%	n	%
Positive	319	56.7	1548	58.7	1867	58.4
Negative	244	43.3	1088	41.3	1332	41.6
Total	563	100.0	2636	100.0	3199	100.0

Table 35.Progesterone receptor (PR) expression by patient age at diagnosis.

Patients were divided into two age groups of ≥40 years and <40 years, and evaluated for PR expression (see Table 35). 57% of patients aged <40 years, and 59% of those aged ≥40 were PRpositive, representing an insignificant difference (p>0.05).

PR expression of patients, whose progesterone receptor expression data and menopausal status data were available in the database, was examined based on menopausal status (see Table 36). 61% of premenopausal patients, and 58% of menopausal patients were PR positive, which was not statistically significant (p>0.05).

Progesterone Receptor	Menopausal status				Total	
	Premenopausal		Postmenopausal			
	n	%	n	%	n	%
Positive	872	60.9	969	57.9	1841	60.4
Negative	559	39.1	706	42.1	1265	39.6
Total	1431	100.0	1675	100.0	3106	100.0

Table 36.Relationship between menopausal status and progesterone receptor (PR) expression in patients with invasive breast cancer.

C) Hormone Receptor (HoR) Expression

Patients diagnosed with invasive breast cancer with expression of at least either of estrogen or progesterone receptors were defined and analyzed as "HoR positive," and those with neither ER nor PR expression as "HoR negative."

Age at diagnosis	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
<40	414	71.3	167	28.7	581	100.0
40 – 49	758	74.0	266	26.0	1024	100.0
50 – 59	628	77.9	178	22.1	806	100.0
60 – 69	405	76.4	125	23.6	530	100.0
≥70	317	81.9	70	18.1	387	100.0
Total	2522	75.8	806	24.2	3328	100.0

Table 37. Hormone receptor (HoR) expression distribution by age at diagnosis in patients with invasive breast cancer (HoR positive: ER and/or PR positive; HoR negative: ER and PR negative).

Hormone receptor (HoR) expressions were classified based on patient age at diagnosis, and examined under two separate groups of HoR positive and negative patients (see Table 37). The percentage of hormone receptor (HoR) positive tumors (76%) was significantly higher (p=0.001) than hormone receptor (HoR) negative tumors (24%).

Patients were divided into two age groups of ≥40 years and <40 years, and hormone receptor (HoR) expression of tumor cells was examined across these groups (see Table 38). Prevalence of HoR positive patients in the ≥40 age group was significantly higher than in the <40 age group (77% vs. 71%, respectively; p=0.005).

HoR status	Age at diagnosis				Total	
	<40 years		≥40 years			
	n	%	n	%	n	%
HoR positive	414	71.3	2108	76.7	2522	75.8
HoR negative	167	28.7	639	23.3	806	24.2
Total	5581	100.0	2747	100.0	3328	100.0

Table 38.Relationship between patient age group and hormone receptor (HoR) expression.

Distribution of HoR expression was examined based on menopausal status in patients with invasive breast cancer, whose hormone receptor data and menopausal status data were available in the database (see Table 39). 75% of premenopausal patients and 76% of menopausal ones were HoRpositive (p>0.05).

Menopausal status	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
Premenopausal	1107	75.2	365	24.8	1472	100.0
Postmenopausal	1349	76.9	405	23.1	1754	100.0
Total	2456	76.1	770	23.9	3226	100.0

Table 39. Hormone receptor (HoR) expression distribution by menopausal status in patients with invasive breast cancer (HoR positive: ER and/or PR positive; HoR negative: ER and PR negative).

Patients were divided into three groups based on pathological tumor diameter, and variations in HoR expression based on tumor diameter were examined (see Table 40). 79% of patients with a pathological tumor diameter of ≤2 cm were HoR positive. However, HoR positive rate decreased inversely proportional to increasing tumor diameter. Similarly, the percentage of HoR negatives rose with increasing pathological tumor diameter. These differences between the groups were statistically significant (p=0.0001).

Tumor diameter (cm)	HoR				Total	
	HoR positive		HoR negative			
	n	%	n	%	n	%
T1 (>2.0)	1205	79.4	312	20.6	1517	100.0
T2 (2.0 – 5.0)	1074	73.5	387	26.5	1461	100.0
T3 (>5.0)	129	68.3	60	31.7	189	100.0
Total	2408	76.0	759	24.0	3167	100.0

Table 40. Hormone receptor (HoR) expression distribution by tumor diameter in patients with invasive breast cancer (HoR positive: ER and/or PR positive; HoR negative: ER and PR negative).

Hormone receptor expressions were evaluated based on pathological lymphatic stage in patients whose pathological lymphatic stage data were available in the database (see Table 41). 77% of pN0 patients, and 69% of pN3 patients were HoR positive (p<0.029, see Table 41A). However, the difference between pN0 and pN+ patients was not significant (see Table 41B).

Pathological Lymphatic Stage	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
N0	966	76.9	290	23.1	1256	100.0
N1	556	78.4	153	21.6	709	100.0
N2	288	76.2	90	23.8	378	100.0
N3	125	68.7	57	31.3	182	100.0
Total	1935	76.6	590	23.4	2525	100.0

Table 41. Hormone receptor (HoR) expression distribution by pathological regional lymphatic stage in patients with invasive breast cancer (HoR positive: ER and/or PR positive; HoR negative: ER and PR negative).

Pathological Lymphatic Stage	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
N0	966	76.9	290	23.1	1256	100.0
N1-3	969	76.4	300	23.6	1269	100.0
Total	1935	76.6	590	23.4	2525	100.0

Table 41A

Pathological Lymphatic Stage	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
N0	966	76.9	290	23.1	1256	100.0
N1-2	844	77.6	243	22.4	1087	100.0
N3	125	68.7	57	31.3	182	100.0
Total	1935	76.6	590	23.4	2525	100.0

Table 41B

Patients registered in the database were classified based on tumor histological grade, and the relationship between various histological grades and hormone receptor (HoR) expressions was investigated (see Table 42). 94% of patients with histological grade I were HoR positive. However, HoR positives decreased with increasing histological grade (HG). These differences between the groups were statistically significant (p=0.0001).

Histological Grade	HoR positive		HoR negative		Total	
	n	%	n	%	n	%
I	108	93.9	7	6.1	115	100.0
II	946	85.3	163	14.7	1109	100.0
III	887	66.1	455	33.9	1342	100.0
Total	1941	75.6	625	24.4	2566	100.0

Table 42. Hormone receptor (HoR) expression distribution by histological grade in patients with invasive breast cancer (HoR positive: ER and/or PR positive; HoR negative: ER and PR negative).

11 HER-2 (c-erb-B2) Expression

23% of patients were HER-2 positive by immunohistochemical analysis (FISH or SISH).

HER-2 Expression	Age at diagnosis					
	<40 years		≥40 years		Total	
	n	%	n	%	n	%
Positive	77	26.5	314	22.2	391	23.0
Negative	214	73.5	1098	77.8	1312	77.0
Total	291	100.0	1412	100.0	1703	100.0

Table 43.HER-2 expression distribution by age at diagnosis in patients with invasive breast cancer.

Patients were divided into two age groups of ≥40 and <40, and the distribution of HER-2 expression in tumor cells was examined across these age groups (see Table 43). 26.5% of younger (<40 years) patients, and 22% of patients aged ≥40 years were HER-2 positive. The difference between the two groups was not statistically significant.

Patients with invasive breast cancer, whose HER-2 expression data and menopausal status data were available in the database, were divided into two groups based on menopausal status, and the distribution of HER-2 expression across these groups was examined (Table 44). 22% of premenopausal patients, and 24% of menopausal ones were HER-2/neu positive (p>0.05).

Menopausal status	HER-2 positive		HER-2 negative		Total	
	n	%	n	%	n	%
Premenopausal	176	22.4	611	77.6	787	100.0
Postmenopausal	215	23.6	695	76.4	910	100.0
Total	391	23.0	1306	77.0	1697	100.0

Table 44.HER-2/neu expression distribution by menopausal status in patients with invasive breast cancer.

Patients were divided into three groups based on pathological tumor diameter (pT1, T2 and T3), and their relationship between HER-2 positive or negative groups was examined (see Table 45). HER-2 expressions by various tumor diameters were 21.5%, 25% and 20%, respectively, which was not statistically significant (p>0.05).

Tumor diameter (cm)	HER-2 positive		HER-2 negative		Total	
	n	%	n	%	n	%
T1 (≤2.0)	172	21.5	628	78.5	800	100.0
T2 (2.1 – 5.0)	186	24.6	569	75.4	755	100.0
T3 (>5.0)	18	20.2	71	79.8	89	100.0
Total	376	22.9	1268	77.1	1644	100.0

Table 45.HER-2 expression distribution by tumor diameter in patients with invasive breast cancer.

The relationship between pathological lymphatic stage and HER-2 positive or negative groups was examined in invasive breast cancer patients, whose HER-2 expression data and pathological lymphatic stage data were available in the database (Table 46). Only 20% of patients without pathological lymphatic involvement (pN0) were HER-2 positive.

Pathological Regional Lymphatic Stage	HER-2 positive		HER-2 negative		Total	
	n	%	n	%	n	%
N0	152	19.6	624	80.4	776	100.0
N1	89	23.8	285	76.2	374	100.0
N2	57	28.1	146	71.9	203	100.0
N3	32	34.0	62	66.0	94	100.0
Total	330	22.8	111.7	77.2	1447	100.0

Table 46.HER-2 expression by pathological regional lymphatic stage in patients with invasive breast cancer.

However, HER-2 positives rose with increasing pathological lymphatic stage. In contrast, percentage of tumors with HER-2 expression declined with increasing lymphatic involvement. These differences between the groups were statistically significant (p=0.0001).

Patients were divided into groups, based on HER-2 expression (i.e. positive or negative), and based on pathological lymph node involvement (pN- and pN+), and the relationship between these groups was examined (see Table 47). Percentage of HER-2 positive patients without lymphatic involvement (20%) was significantly lower than that of HER-2 positive patientswith lymphatic involvement (pN+) (26.5%) (p=0.002). Similarly, percentage of HER-2 negative patients decreased with increasing lymphatic involvement.

Pathological Lymphatic Stage	HER-2 positive		HER-2 negative		Total	
	n	%	n	%	n	%
N0	152	19.6	624	80.4	776	100.0
N1, 2, 3	178	26.5	493	73.5	671	100.0
Total	330	22.8	1117	77.2	1447	100.0

Table 47.Relationship between presence of HER-2 expression and pathological regional lymphatic involvement in patients diagnosed with invasive breast cancer.

The relationship between HER-2 expression and histological grade was examined in patients with invasive breast cancer, for whom these data were available in the database (see Table 48). Only 10% of patients with histological grade I were HER-2 positive. HER-2 positives rose with increasing histological grade. This relationship was statistically significant (p=0.0001).

Histological Grade	HER-2 positive		HER-2 negative		Total	
	n	%	n	%	n	%
I	7	10.0	63	90.0	70	100.0
II	84	15.4	461	84.6	545	100.0
III	207	28.2	526	71.8	733	100.0
Total	298	22.1	1050	77.9	1348	100.0

Table 48.HER-2 expression by histological grade in patients with invasive breast cancer.

12 Molecular Subtypes

Invasive cancer patients with full data on estrogen receptor (ER), progesterone receptor (PR) and HER-2 receptor expression available in the database had the following molecular subtypes (see Table 49): Luminal A (ER and/or PR positive, HER-2 negative) 62%, Luminal B (ER and/or PR positive, HER-2 positive) 15%, HER-2 Group (ER and PR negative, HER-2 positive) 8.5%, and Triple Negative Group (TNG – ER, PR and HER-2 negative) 15%. The likelihood of a patient to be molecule subtype Luminal A grew by increasing age at diagnosis, which was statistically significant (p=0.006). However, analyses showed no significant relationship between other breast cancer molecular subtypes and age at diagnosis.

Age at diagnosis	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
<40	160	55.7	53	18.5	24	8.4	50	17.4	287	100.0
40 – 49	331	62.3	75	14.1	37	7.0	88	16.6	531	100.0
50 – 59	271	62.7	63	14.6	45	10.4	53	12.3	432	100.0
60 – 69	161	63.1	30	11.8	24	9.4	40	15.7	255	100.0
≥70	131	70.1	26	13.9	14	7.5	16	8.6	187	100.0
Total	1054	62.3	247	14.6	144	8.5	247	14.6	1692	100.0

Table 49. Distribution of molecular subtypes by age at diagnosis in patients with invasive breast cancer – Lum A: Luminal A; Lum B: Luminal B; TNG: Triple Negative Group

To more closely examine the distribution of molecular subtypes, patients were divided into two age groups of ≥40 and <40, and the distribution of tumor cell molecular subtypes across these groups was examined (see Table 50). 64% of tumors in group Luminal A were in patients aged ≥40 years. However, the percentage of Luminal B and triple negative group (TNG) tumors was higher in the <40 years age group. This difference between the groups was statistically significant (p=0.044). Percentage of HER-2 positive patients were comparable in both age groups.

Tumor molecular subtype	Age at diagnosis					
	<40 years		≥40 years		Total	
	n	%	n	%	n	%
Lum-A	160	55.7	894	63.6	1054	62.3
Lum-B	53	18.5	194	13.8	247	14.6
HER-2	24	8.4	120	8.5	144	8.5
TNG	50	17.4	197	14.0	247	14.6
Total	287	100.0	1405	100.0	1692	100.0

Table 50.Distribution of tumor molecular subtypes by age at diagnosis in patients with invasive breast cancer.

The relationship between molecular subtype and menopausal status was examined (see Table 51). No significant relationship was found between breast cancer molecular subtype and menopausal status (p>0.05).

Menopausal status	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
Premenopausal	476	61.1	119	15.3	57	7.3	127	16.3	779	100.0
Menopausal	572	63.1	128	14.1	87	9.6	120	13.2	907	100.0
Total	1048	62.2	247	14.7	144	8.5	247	14.7	1686	100.0

Table 51.Relationship between tumor molecular subtype and menopausal status in patients with invasive breast cancer.

The relationship between molecular subtype and pathological diameter was examined (see Table 52). 66% of patients with pathological tumor diameter ≤2 cm were luminal A, 15% were luminal B, 6% were HER-2 positive, and 12% were in the TNG. The percentage of patients with molecular subtype luminal A and B decreased with increasing tumor diameter. In contrast, the percentage of HER-2 positive patients and those in the TNG increased with tumor diameter. These differences between the groups were statistically significant (p=0.0001).

Tumor diameter (cm)	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
T1 (<2.0)	525	66.1	121	15.2	51	6.4	97	12.2	794	100.0
T2 (2.0 – 5.0)	449	59.6	111	14.7	75	10.0	118	15.7	753	100.0
T3 (>5.0)	49	55.1	8	9.0	10	11.2	22	24.7	89	100.0
Total	1023	62.5	240	14.7	136	8.3	237	14.5	1636	100.0

Table 52.Relationship between tumor diameter and breast cancer subtype in patients with invasive breast cancer.

The relationship between molecular subtype and pathological lymphatic stage was examined in patients with invasive breast cancer (see Table 53). 64% of patients without lymphatic involvement (pN-) were Luminal A, 13.5% were Luminal B, 6% were HER-2 positive, and 17% were in the TNG. Based on an independent examination of molecular subtype variables, the percentage of Luminal A tumors decreased, but HER-2 tumors increased with increasing lymphatic involvement stage. These changes were statistically significant (p=0.001). However, no significant relationship was observed between molecular subtypes Luminal B and TNG, and changes in the level of lymphatic involvement. Considering all molecular subtypes, a statistically significant relationship was not observed between molecular subtypes and the level of lymphatic involvement.

Pathological Lymphatic Stage	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
N0	491	63.6	104	13.5	48	6.2	129	16.7	772	100.0
N1	239	64.2	57	15.3	32	8.6	44	11.8	372	100.0
N2	121	59.6	33	16.3	24	11.8	25	12.3	203	100.0
N3	44	46.8	15	16.0	17	18.1	18	19.1	94	100.0
Total	895	62.1	209	14.5	121	8.4	216	15.0	1441	100.0

Table 53. Distribution of breast cancer subtypes by regional lymphatic stage.

Patients were divided into four groups based on molecular subtypes, and into two groups based on pathological lymph node involvement (pN0 and pN+), and relationships between these groups were examined (see Table 54). There were statistically significant (p=0.002) changes in percentages of all breast cancer molecular subtypes in both groups of patients, with and without lymphatic involvement. pN0 patients had a greater percentage of tumors of molecular subtypes Luminal A and TNG, but fewer of tumors of molecular subtypes Luminal B and HER-2. However, considering all groups as a whole, there was no increasing or decreasing trend with any of the molecular subtypes, with or without lymphatic involvement.

Pathological Lymphatic Stage	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
N0	491	63.6	104	13.5	48	6.2	129	16.7	772	100.0
N1-3	404	60.4	105	15.7	73	10.9	87	13.0	669	100.0
Total	895	62.1	209	14.5	121	8.4	216	15.0	1441	100.0

Table 54.Relationship between patient molecular subtype and pathological regional lymphatic involvement.

Variation of molecular subtypes with histological grade was investigated (see Table 55). 87% of patients with histological grade I were in molecular subtype group Luminal A, 10% were in Luminal B, and 3% were in TNG. There was a reduction in the percentage of tumors of phenotype luminal A with increasing histological grade.

Histological Grade	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
I	61	87.1	7	10.0	0	0	2	2.9	70	100.0
II	428	79.1	63	11.6	21	3.9	29	5.4	541	100.0
III	366	50.1	111	15.2	96	13.2	157	21.5	730	100.0
Total	855	63.8	181	13.5	117	8.7	188	14.0	1341	100.0

Table 55. Distribution of breast cancer subtypes by patient histological grade.

However, percentage of tumors in groups Luminal B, HER-2 positive and TNG increased with increasing HG. This relationship between the groups was statistically significant (HGI and HGII+III, p=0.0001, see Table 56).

Histological Grade	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
I	61	87.1	7	10.0	0	0	2	2.9	70	100.0
II+III	794	62.5	174	13.7	117	9.2	186	14.6	1271	100.0
Total	855	63.8	181	13.5	117	8.7	188	14.0	1341	100.0

Table 56. Relationship between Histological Grade (I and II+III) andmolecular subtype in patients diagnosed with invasive breast cancer.

Tumors detected in patients were divided into two groups based on grade (I+II and III) (see Table 57) and their relationship with molecular subtype was reanalyzed, which gave the same statistically significant result (p=0.0001) for the groups, as depicted in Table 56.

Histological Grade	Lum A		Lum B		HER-2		TNG		Total	
	n	%	n	%	n	%	n	%	n	%
I+II	489	80.0	70	11.5	21	3.4	31	5.1	611	100.0
III	366	50.1	111	15.2	96	13.2	157	21.5	730	100.0
Total	855	63.8	181	13.5	117	8.7	188	14.0	1341	100.0

Table 57. Relationship between Histological Grade (I+II and III) and molecular subtype in patients diagnosed with invasive breast cancer.

Discussion

Breast Cancer Incidence and Mortality Rate in Turkey and in the World

With the growing incidence and mortality rate of cancer, the disease is now the cause of one in every eight deaths around the world, rapidly gaining the character of a global epidemic. At current rapid growth rate, number of new cancer patients will double by 2030, reaching 21.4 million from 12.7 million calculated in 2008. Similarly, the number of patients dying of cancer will increase to 13.5 million from 7.6 million (4). When developed and developing countries are examined separately, we can see that cancer incidence and mortality rates in developing countries are increasing at a much faster rate than in the developed world.

An estimated56% of newly diagnosed cancers and 63% of cancer deaths occur in developing countries (4,7). According to the World Health Organization (WHO), the burden on low- and medium-income countries from cancer and other chronic conditions is greater than that on developed countries, since there these conditions develop at earlier ages, preventable complications cannot be dealt with, and patients die far earlier, driving up the economic burden of disease even further. According to calculations, in year 2008 early deaths and complications have caused an estimated trillion dollar loss (29). Important causes of the growing incidence and mortality rate of cancer in the developing world include lack of access to sufficient information, lack of protection, early detection and treatment means, and absence of adequate medical and public health infrastructures, which results in diagnosis at the advanced stage, inadequate treatment of patients, and substantial problems due to absence of sufficient palliative care. A holistic approach covering improved prevention, early detection, treatment and pain management will help save lives and mitigate cancer complications.

Breast Cancer in Turkey and in the World

Breast cancer is the most common type of cancer in women and it accounts for approximately a fourth of all cancers. According to Globocan 2008 data, total number of patients diagnosed with breast cancer around the world is 1,400,000, half of whom reside in developed countries (4). According to, again, Globocan data, the figure was 1,150,000 in 2002, representing a 17% increase in the breast cancer incidence over six years (4,7). The increase rate of breast cancer incidence in developing countries over six years was 26%, compared to 8% in developed countries. In the years ahead, breast cancer incidence is projected to decline further, in particular with the reduced use of hormone replacement therapy and preventive measures.

In Turkey, the incidence of breast cancer is increasing rapidly. The breast cancer incidence has reached an estimated 50 per 100,000 in 2010, from 24.1 per 100,000, according to a 1993 study, representing a more than 2-fold increase in breast cancer incidence in Turkey over the past 20 years (5,6,21,28). Breast cancer is the most common cause of female deaths, accounting for 13.7% of all female cancer mortalities (4,5,6), followed second by lung cancer with 12.8%. The number of global female deaths from breast cancer rose to 458,000 in 2008 from 411,000 in 2002, representing a 10% increase in the mortality rate over six years (4). During the same period, mortality rate in developed countries declined by 1% in contrast to a 18% increase in the developing world.

Gender

The female gender is an important risk factor for breast cancer, which is 150-times more common in women than men (4). 99% of all breast cancers occur in women. Our data,also show that 99% of breast cancers occur in women and 1% in men, similar to other examples around the world.

Age

Breast Cancer Distribution by Age

6.6% of US women with breast cancer are below the age of 40, 2.4% are below the age of 35, and 1% are below the age of 30 (see Figure 19) (35). According to ACS (American Cancer Society) data, only 5% of new breast cancer cases reported between years 2002 and 2006 were in patients aged less than 40 years (36). The ratios are similar in Western Europe and other developed countries. In our study, the percentage of women with breast cancer aged less than 40 years was 17%. Breast cancer percentages in age groups <35 and <30 were 7.4% and 2.2%, respectively, which is almost three times higher than the younger

agebreast cancer rate in the US. Percentage of breast cancers at younger age (≤40 years) is higher in Asian and African countries, reaching 30% (37). The reason is Turkey and other developing countries have a younger population and, hence, a higher ratio of youths to elders. According to Turkish Statistical Institute (TÜİK) data, female population below the age of 40 constitute 68% of total female population in Turkey (38), compared to approximately 45% in the US (39). This difference indicates that in Turkey the concentrationof population is higher on the younger segment, which explains the relatively higher rate of cancers at younger age. Similarly, the percentage of breast cancer patients aged >65 years was 17.7% in our study, compared to 33% in the US, again explained by an older US population and higher incidence of breast cancer (39).

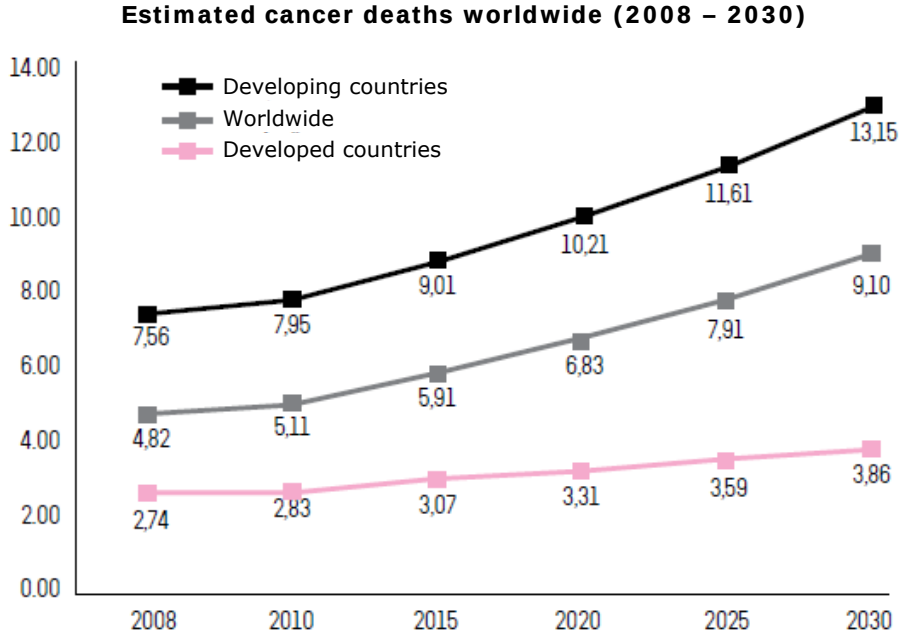


Figure 19. Estimated cancer deaths worldwide, in developing countries and in developed countries, according to IARC Globocan data and predictions.[29]
(http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=792)

Looking at the age at diagnosis curve, we see an interesting graphic, markedly different from that of the Western World (Figure 10). By age groups, breast cancer incidence peaked at 45 – 49 years (constituting 16.7% of all patients), began declining to its lowest point at 65 – 69 years with 7.6%, and rose back to 10% at 70 years age group. In the US, however, breast cancer incidence exhibit a sigmoid shape, increasing after the age of 40, climbing rapidly after 50 years of age to peak at 75 – 79 years age group, and then decline again after the age of 80 (see Figure 18).

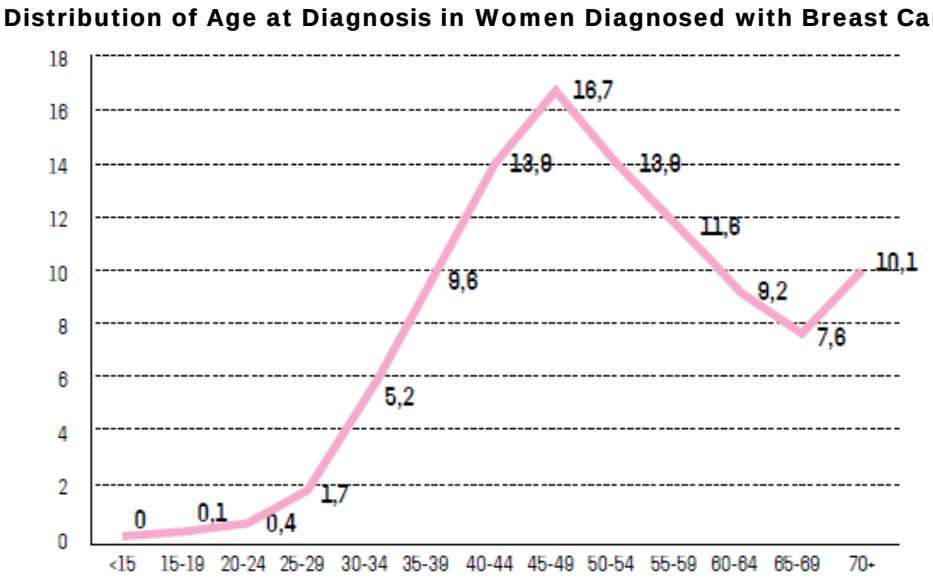


Figure 10.Breast cancer incidence by age at diagnosis (%).

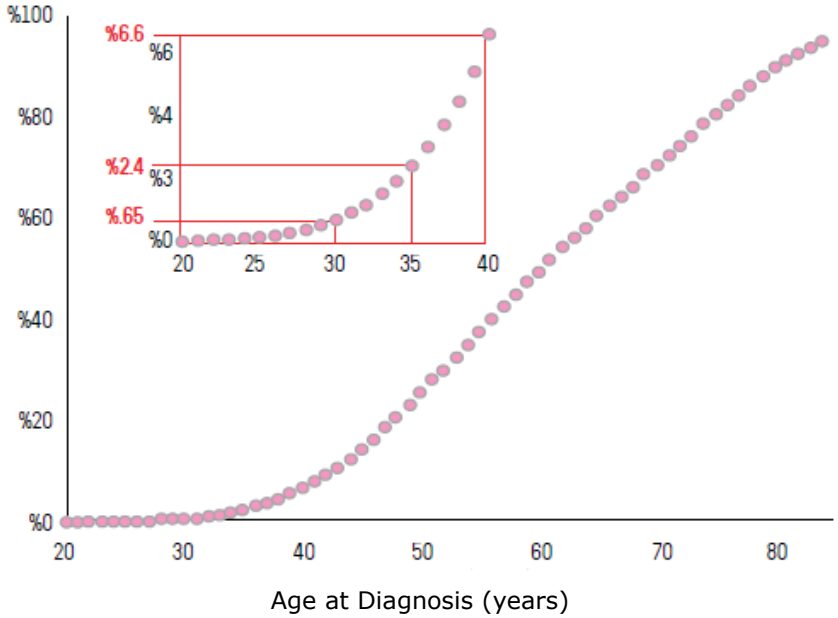


Figure 18. Distribution of breast cancer incidence by age group in the US (Cumulative percent of breast cancer in females, SEER17, 2000-2005).

In women diagnosed with invasive breast cancer, the median age at diagnosis was 50 (12 – 97 years). According to American Cancer Society (ACS) data covering the period between years 1998 and 2002, the median age for breast cancer is 61 in the US (36). This difference is explained by the older population of the United States.

Due to younger population of Turkey, the ratio of premenopausal women with breast cancer is high, around 45%, similar to cancer concentration in the <40 age group. In the US and Western Europe, however, only 25% of women diagnosed with breast cancer are menopausal (40). The higher rates of premenopausal and younger-age breast cancer cause a higher rate of invasive ductal cancer, which has poor prognosis, and later clinical and pathological stage at diagnosis in this age group.

Hormones of ovarian origin (i.e. estrogen and progesterone) are the key determinants of breast cancer in women (41). Breast tissue is exposed to these hormones at increasing and decreasing degrees over life. However, age is a key indicator of the beginning of ovarian activity (i.e. menarche) and its end (i.e. menopause) (42). Reproductive breast cancer risk factors (i.e. menarche, first birth age, and menopause) is related to encountering, in particular, estrogen in a woman's life. A first menstruation (menarche) age of ≤12 in women increases the risk for breast cancer, with the risk decreasing by 10% for every two years of delayed menarche (41). Giving birth at a younger age also mitigates the risk of breast cancer. This protective effect is independent from the number of deliveries. Risk of breast cancer is higher in women who give first birth after the age of 30 than in women who never gave birth. The protective effect of giving birth at a younger age is explained by terminal end buds' transforming to secretory units with lower proliferative activity and more effective DNA repairing ability, induced by pregnancy and lactation. Similarly, longer exposure to hormones increases the risk of breast cancer at late menopause (>55 years of age). Risk of breast cancer is twice as low in women entering menopause before the age of 45, compared to women entering menopause after 55 years of age. Our study of breast cancer risk factors also confirm increased risk of breast cancer from late birth (>35 years) and age >50 years (31).

Increasing age is the primary risk factor in women or developing breast cancer (41). In developed countries, the risk of developing breast cancer was 0.4% in women aged ≤39 years (1 in every 210 women), 3.86% in women aged 40 to 59 years (1 in every 26 women), 3.51% in women aged 60 to 69 years (1 in every 28 women), and 6.95% in women aged ≥70 years (1 in every 15 women) (43). Obviously, the commonly known ratio of 12.28%, i.e. "a woman's risk of contracting breast cancer in her lifetime" (1 in every 8 women), predominantly stems from the higher risk percentages in older women, and the risk of developing breast cancer is less than only 4% in premenopausal women. Because developed countries haveyounger populations, their breast cancer incidence is lower. However, a growing population, and Westernized lifestyles (e.g. diet, reproductive factors, overweightness, sedentary lifestyles, etc.) are causing breast cancer incidence and mortality rates to gradually rise (10). In Turkey, breast cancer incidence and mortality rates vary between eastern and western regions. In Marmara and Aegean Regions, where people lead more westernized lifestyles, the incidence of breast cancer is 50 per 100,000, percentage of early-stage (stages I and II) breast cancers is 65 to 75%, and 5-year mortality rate is 10 to 15%, compared to 25 per 100,000, 25 to 40%, and 35%, respectively, in East and Southeast Anatolia Regions (5,6,30). Factors driving high rates of breast cancer mortalities include late detection, lack of awareness, lack of education, difficulties in accessing diagnostic and therapeutic careand shortcomings.

Breast cancer is an age-related and heterogeneous type of tumor (44). Normal breast tissue undergoes various changes due to menopause and aging through a woman's life phases. However, the effect of aging on breast cancer biology has not been fully elucidated. While breast cancers occurring at earlier ages are thought to be associated with causes that result in usually hereditary or acquired transformation of the unmatured breast epithelium, breast cancers occurring at later ages are presumed to be associated with long-term exposure to factors that cause the transformation of non-aged, susceptible breast epithelial tissue (44). In developed countries, breast cancer incidence by age rise exponentially until menopause, and then slow down, which may be explained by an overlap of earlier-age and later-age tumor (44). In our breast cancer incidence profile by age, however, breast cancer incidence does rise exponentially until menopause,

but then begin declining, different from that in developed countries, to rise back after the age of 70 (see Figure 1). This difference is explained by Turkey's young population.

Steady rise of breast cancer incidence in developed countries until the age of 80 years suggests a tumorigenic predisposition of aging breast tissue (45). However, studies for elucidating the underlying molecular biology and genetics are still at their infancy stage, although very significant discoveries were made. The timing of carcinogenic events and the reason behind the aging breast epithelium's exposure to transformation remain unknown (46). There have been some advances in cell division cycle, mechanisms of DNA damage and repair, and apoptosis for explaining the relationship between aging and cancer at the cell level. However, the questions of whether breast cancers emerging at later ages are caused by senescent stromal cells or epithelial cells, and whether cancer-aging hypotheses can clinically predict breast cancer behavior remain unanswered.

In the case of women aged less than 40 years who were diagnosed with cancer and who have a familial history of the disease, it is recommended to assess them or their first degree relatives for risk. For this purpose, we need to establish "High-Risk Patient" clinics within breast units across the country. Methods that can be used risk assessment may be discussed under three headings: 1. Models for mathematical calculation of probability (Gail and Claus models), 2. Models for calculating probability of genetic mutation (BRCAPro and others), and 3. Genetic tests (47-50). Currently, we do not have standard criteria for determining whom to apply genetic tests to. However, various US institutions/agencies, such as the National Comprehensive Cancer Network (NCCN), the American College of Medical Genetics (ACMMG), and U.S. Preventive Services Task Force (USPSTF), do have suggestions for the required steps to follow in these individuals (51-53). Monitoring, surgical and systemic therapeutic and/or chemoprevention options may change for women with cancer who are carriers of breast mutation or healthy women who are carriers of a significant mutation, depending on the results of genetic testing. Genetic test results should be assessed at institutions with a familial cancer clinic wherea multidisciplinary staff of experts interested in the field are available, and clinicians should explain monitoring/therapeutic options available to individuals being tested.

It was previously discussed that in developing countries, breast cancer was rare among younger women, in contrast to the situation in Turkey. However, it is necessary to discuss, to some degree, the limits of young age which are deemed high-risk for breast cancer. Various studies characterize women below the age of 35, 40 or 45 years as "young" women/patients (54-56). A study has noted that the age limit where the risk begins to rise is 40 years, considering that the risk of breast cancer in women aged less than 40 years is around 1%, and only 7% of all breast cancers occur in women under the age of 40 years (54). Another important reason why the age of 40 years is used as the limit between earlier and later ages is that it is the recommended age at which to begin screening healthy women for potential breast cancer developments (54). At present, a majority of the evidence available point out that mammographic screening programs reduce breast cancer deaths in womenaged 40 to 74 years (41). Despite the debate on this issue in recent years, the National Cancer Institute, the National Cancer Society, the Radiological Society of North America, and the National Comprehensive Cancer Network (NCCN) recommend yearly mammographic examinations in women aged 40 years and older (41). The Anti-cancer Bureau in Turkey, however, recommends biannual mammographic screens from the age of 50 years, as in the European Union countries. However, as discussed above, 40 years of age is considered to be a more appropriate point

to begin mammographic screening, given that about one half (48%) of women with breast cancer are under the age of 50 in Turkey. The results from Mammographic Screening Project, which we initiated in Bahçeşehir, Istanbul in year 2008 covering approximately 6,000 women over 10 years, will help us better understand whether screening is viable and economic in developing countries like ours. Women residing in that region are invited to the screening center where they undergo physical examination and mammography. Where appropriate, ultrasonography and biopsy are used for diagnosis. This entire process is provided without charge. Between years 2009 and 2012, 6,500 women were screened, and 56% of women who underwent screening, and 58% of those who were diagnosed with early-stage breast cancer (45 women) were in the 40-49 age group.

Various studies have shown younger age to be an independent and poor prognostic factor for breast cancer (54,57-60). Also, according to SEER data, risk of death from breast cancer is 39% higher in women aged less than 40 years, compared to women older than 40 (54). Comparing these two age groups, we find that the most significant difference in the mortality rate is at early-stage breast cancer. In women aged less than 40 years who were diagnosed with breast cancer, the mortality rate from breast cancer is 44% higher for Stage I breast cancer, and 9% higher for Stage II breast cancer, compared to the group aged more than 40 years. More malignant tumor properties and higher frequency of triple negative breast cancer drive a higher mortality rate from younger-age breast cancer. Consequently, special care should be taken with younger-age breast cancer, which is more common in Turkey, striving for early-detection and effective treatment. In this age group, various potential advantages exist from detecting breast cancer at an early stage: 1. Younger women have longer life expectancy, 2. In younger women, it takes less time for breast cancer to grow from a screenablesize to clinical manifestation, 3. Missed diagnosis of breast cancer in younger women is the most frequent cause of malpractice actions brought against surgeons by breast cancer patients in developed countries (54).

Invasive ductal carcinoma has poorer prognosis than invasive lobular carcinoma and other specific histological types of breast cancer (62). According to our data, 85% of women aged <40 years were diagnosed with invasive ductal carcinoma, 15% with invasive lobular and mixed-type invasive cancer, compared to 81% and 19%, respectively, in women aged >40 years (see Table 5). This finding indicates a higher percentage of invasive ductal cancers in younger women.

Diagnosis of clinically advanced-stage breast cancer in younger patients is associated with not using mammography as a screening method in these women, and a high false-positive rate of clinical examination and radiological diagnostic methods due to high breast density (54). Percentage of Clinical Stage I breast cancers were 21% in patients aged <40 years, and 29% in the 50-59 age group. Stage III breast cancers were 19% in the <40 age group and 13% in the 50-59 age group (see Table 15). An interesting findings was noted in women aged >70 years: in this group also, the percentage of Clinical Stage I breast cancers at diagnosis was higher than in the <40 age group (26%), but lower than in the 50-59 age group (see Figures 3,4). Diagnosis of advanced stage disease in the later age groups can be explained by denial of disease, and the mass in the breast being often non-painful; in fact, Turkish women usually have the misconception that non-painful masses within breasts are benign. Diagnosing of breast cancer at late-stage in younger women causes a tumor diameter to be larger compared to later age groups. In younger patients (aged <40 years) the mean tumor diameter was 2.8 cm, compared to 2.4 in the 40-69 age group (see Table 17). The percentage of pathological T1s (≤2 cm) was 42% in the <40 age group, and 50% in the 40-69 age group. Similarly, the percentage of pT3s (>5 cm) was 9%

in patients aged <40 years, and 4% in the 50-59 age group (See Table 18). Looking at pathological tumor stage by age group, we see a similar situation (see Table 28). The percentage of pathological stage I breast cancers were 22% in the <40 age group, and 30% in the 50-59 age group. The percentage of pathological Stage III breast cancers was 26% in the <40 age group and 19% in the 50-59 age group. When we compare these two age groups for Stage III and IV, we find similar rates (28.5% and 22.5%, respectively; Table 29).

It was found that patients diagnosed with breast cancer at a younger age had higher rates of axillary positives, higher histological grade, lower rates of estrogen and progesterone positives, and higher rates of HER-2 positives (54-61). In the database, the percentage of pathological axillary negatives (44%) were lower in patients aged <40 years, compared to those in later age groups (55% in the 60-69 age group, and 56% in the >70 age group). Similarly, percentage of HG III breast cancers was 60% in the <40 age group, and 44% in the 60-69 age group (see Table 31). Comparing the <40 age group with ≥40 age group for HG III, we find that these rates were 60% and 48%, respectively (see Table 32).

In breast cancer patients, hormone receptor (ER, PR) positives increased with age. In younger patients the percentage of estrogen receptor (ER) positives was 61%, compared to 71% in the ≥40 age group (see Table 36). However, the difference is smaller with progesterone receptor positives (57% vs. 59%, see Table 38). Looking at patients who were positive for both or either of ER and PR, the percentage of positives was 71% in the <40 age group, which increased with age, peaking at the >70 age group (82%, see Table 40). Comparing this percentage for ages <40 and ≥40, we find 71% and 77%, respectively (see Table 41).

23% of patients with HER-2 expression data available in the database were positive for this parameter, and this percentage was higher in the <40 age group (26.5%).

Breast cancer is examined under four different molecular groups (63,64). In the group Luminal A ER and PR are positive, and HER-2 is negative; in Luminal B ER and PR and HER-2 are all positive. Luminal A and B account for 70 to 75% of all breast cancers. In the HER-2 group, ER and PR are negative, and HER-2 is positive, and 10 to 15% of all breast cancers fall within this group. In the triple negative group (TNG), ER, PR and HER-2 are negative, accounting for 20 to 30% of all molecular subtypes. From a prognostic viewpoint, Luminal A has the best and TNG has the worst prognosis. In our database, the percentages of patients with molecular subtypes Luminal, Luminal B, HER-2 and TNG were 62%, 15%, 8% and 15%, respectively. Compared to Western societies, we find that Turkish patients had lower rates of breast cancers of molecular subtypes HER-2 and TNG.

The percentages of Luminal A, Luminal B, HER-2 and TNG breast cancers in our patients in the <40 age group were 56%, 18.5%, 8% and 17%, respectively. In the later age group (50-59 years), the percentages were 63%, 15%, 10% and 12%, respectively. These data show that the percentage of molecular subtypes with poorer prognosis in younger patients was significantly higher. The difference is more manifest in the >70 age group, 7.5% of whom were HER-2 positive, and 8.8% were in the TNG. Thus, breast cancers of type TNG accounted for one half of the <40 age group (see Table 56).

Menopausal Status

Turkish population is notably younger than that of developed countries. As discussed above, women under the age of 40 constitutes approximately 68% of total female population in Turkey (38). In the US, however, women under the

age of 40 constitute about 45% of the total female population (21). 45% of women in our database were premenopausal, compared to 20 to 25% in Western societies (54-55). Looking at tumor histological types versus menopausal status of patients, we find no difference between them (see Table 6). However, looking at clinical stage versus menopausal status, we see that premenopausal patients had a lower percentage of stage I breast cancers, buta higher percentage of stage III breast cancers, compared to menopausal patients (see Table 16). Higher breast density in premenopausal patients cause late clinical and radiological detection of the tumor, resulting in more advanced stage diagnoses. The same outlook is present in tumor stages. The percentages of pT1s and pT3s in premenopausal women were 47% and 7%, respectively, compared to 49% and 5% in menopausal women, respectively (see Table 20). The outlook is less favorable in premenopausal women also in terms of axillary lymphatic involvement. In this group, the percentage of pN0 was 47%, compared to 53% in the menopausal group, and the lymphatic involvement rate is also higher in the premenopausal group (see Tables 24 and 25). Although a difference favoring the menopausal group exists between these groups in terms of pathological stage, it was not very significant (see Table 30). Percentage of ER positives was significantly higher in the menopausal group (73% vs. 66%, see Table 37). The opposite is true for PR. 61% of premenopausal patients were PR positive, compared to 58% in the menopausal group (see Table 39). Either hormone receptor (HoR) positives and HER-2 positives were similar in both groups (see Tables 42 and 47). Compared based on molecular subtypes, the percentages of Luminal A and B breast cancers were close in both groups. However, HER-2 positive (10% vs. 7%) and triple negative (16% vs. 13%) breast cancers were slightly higher in the menopausal group (see Table 54).

Histological Type

Broader use of community-based screens result in a higher rate of in-situ breast cancers. Before routine use of mammographic screening, ductal carcinoma in situ (DCIS) could be detected only when it was palpable, and constituted only 1% of total breast cancers (65). At present, it is usually detected although non-palpable, and constitute 20 to 25% of newly diagnosed breast cancers (65). In the US, approximately 288,000 new cases of breast cancer were reported (61), including 230,000 invasive, and 58,000 (20%) in situ breast cancers. 85% of in situ cancers were DCIS. In mammograms, DCIS usually appears in the form of clustered pleomorphic microcalcifications. In Turkey, due to lack of community-based organized mammographic screens, cases of DCIS constitute approximately 5% of total breast cancer cases registered in our database. Enhanced and generalized use organized, community-based mammographic screens, like the one we conducted in Bahçeşehir, will increase the detection rate of DCIS. In fact, in the screen that we conducted between years 2009 and 2012 covering 6,500 women, 21% of the 45 cases of breast cancer detected were DCIS, and 61% were stage I breast cancers.

Identifying the histopathological type of breast adenocarcinomas is also highly important as it indicates intrinsic characteristics of tumor cells and helps determine the prognosis. Breast adenocarcinomas with different clinical outlooks and/or survival differences do exhibit different specific structural and cytological patterns at the microscopic level. The latest breast cancer classification of the World Health Organization (WHO) posted in year 2003 included 17 histological special types of breast cancer (66,67). The most common type was "invasive ductal carcinoma," which comprised 49 to 75% of all invasive cancers in different datasets (62,66-67). In our dataset, the histological types of breast cancer were as follows: IDC 79%, ILC 7%, IMC 10%, and other special histological types 4%. As can be seen, invasive ductal cancers constitute 79% of all invasive cancers;

they frequently form a palpable mass and exhibit mammographic density. This histological type has the worst prognosis (62).

The second most frequent histological type of breast cancer, after invasive ductal carcinoma (IDC), is invasive lobular carcinoma (ILC) (62,66). Different trends are developing over time between histological types of breast cancer. In the US, the incidence of ILC steadily increased between years 1987 and 1995, and constituted 16% of all breast cancers detected in 1999 (67). However, the incidence of IDC remained unchanged over the same period.

Similar changes were observed in various European countries in the incidence rate of breast cancer histological types (66). This rise in the incidence of IDC, although it more difficult to clinically detect it than IDC, is mainly associated with postmenopausal hormone replacement therapy. However, after it was shown in a 2002 study published by Women Health Initiative (WHI) that combined HRT increased the incidence of breast cancer and coronary heart disease, the use of HRT declined by more than 80%, with an associated 7% drop in breast cancer incidence. This decline was more significant for ILC (68-71). The risk for the cancer to be multifocal and bilateral is higher. In our dataset, invasive lobular cancers constitute 7% of total breast cancers, similar to other datasets.

Diagnosing ILC involves a number of difficulties. Mammographic sensitivity is low, and the ratio of false-negatives is high (70). Ultrasonography also has low sensitivity and specificity particularly for smaller tumors (71). Magnetic resonance imaging (MRI) has a high accuracy rate in detecting these types of tumors. Because of the difficulty of localizing ILC lesions and their low cellularity, false negatives are possible with core biopsy as well (73).

Various studies have demonstrated that tumors with ILC histology are a separate disease entity with different clinical and biological characteristics compared to IDC tumors (66-70). Risk factors for developing ILC also differ in various respects from IDC risk factors (87,71). In patients with ILC, positive estrogen and progesterone receptor expression is higher than in patients with IDC (66-72). One of the reasons for hormone replacement therapy to cause an increase in ILC tumors in particular is thought to be this increase in hormone receptor expressions (69). Similar to the above studies, the percentage of estrogen receptor positive patients in the database diagnosed with ILC or IMC was statistically significantly higher than in the group with IDC ($p=0.0001$).

ILC usually occurs in older patients, and the tumor diameter at diagnosis is larger than in patients with IDC (60,67). Higher percentage of ILC in older patients may be associated with the low proliferation rate of these tumors and difficulties involved in clinically detecting them. Tumor histological type is aclinico-pathological factor worked for predicting axillary lymph node involvement, and the metastasis frequency of invasive ductal carcinoma to lymph nodes was higher than with invasive lobular carcinomas and other invasive cancers (62,67). However, a study by Lorfida et al. (73) found that prognosis for patients with invasive lobular cancers was poorer than that for patients with invasive ductal carcinoma. The same factors may explain the high rate of ILC in patients who were metastatic at diagnosis. In our database, 15% of patients with histological type ILC+IMC, and 19% of those with IDC were in the <40 age group. Although, in patients with ILC, the tumor diameter at diagnosis was larger than that in patients with IDC, the percentage of lymphatic involvement waslower in patients with ILC (62,64,67). The percentage of axillary involvement at diagnosis was 41% in patients diagnosed with IDC, and 59% in those with ILC+IMC, similar to the rates reported in literature. Tumor histological types and histological grades were comparable in premenopausal and postmenopausal patients (see Tables 6 and 8). Looking at pathological stage at diagnosis, we find

that patients with histological types ILC+IMC were in more advanced stages. In patients diagnosed with IDC, the percentage of pathological stage I and II breast cancers was 76.5%, and ILC+IMCs 68% in patients diagnosed with IDC (see Table 9). Looking at pathological tumor diameters, we find that 92% of patients diagnosed with ILC+IMC, and 95% of those with IDC had a tumor diameter of <5 cm (see Table 10).

Gene amplification and/or enhanced expression of HER-2, reported in 20 to 30% of patients with invasive breast cancer, are known to be associated with reduction in overall survival and disease-free survival and reduced response to chemotherapy (78). Various studies have found that ILC tumors were frequently ER and PR positive, HER-2 negative, bcl-2 positive and p53 negative (79). Further, because proliferative activity and lymphatic vascular invasion rates were lower and vascular endothelial growth factor (VEGF) expression is at minimal levels, it was found that ILC tumors had better biological characteristics than IDCs (80). Similar to above findings, our study also found that HER-2 positive tumors of histopathological type IDC were approximately nine-fold more frequent than ILC and IMC ones, representing a statistically significant difference (p=0.0001) (see Table 11). Percentage of HER-2 positives was 24.5% in patients diagnosed with IDC, and 14% in those with ILC or IMC. In other words, 86% of ILC or IMC tumors did not exhibit HER-2 expression, while IDCs had a higher rate of positives, which was statistically significant (p=0.0001, see Table 12).

80% of ER positive patients were diagnosed with IDC, and 20% with ILC+IMC (see Table 13), compared to 87% and 13%, respectively,in ER negative patients. ER positive tumors had a higher rate of IDC histopathology than ER negative ones, which was statistically significant (p=0.0001). However, a large majority of tumors observed in both IDC and ILC+IMC groups were ER positive (see Table 14). The percentage of ER positives was 68% in patients with IDC, and 78% in those with ILC+IMC, representing a statistically significant difference (p=0.0001).

17% of patients registered in our breast cancer database were below the age of 40 years. As discussed earlier, this high rate is mainly related to younger population of Turkey. However, an important point that needs to be considered when evaluating women who contract breast cancer at earlier age is that, incidence of inherited cancers is higher in this age group (75,76). It was found that tumors detected in carriers of cancer-susceptibility genes may carry different histological phenotypes, which applies for breast cancer as well. Deciding which women diagnosed with breast cancer to recommend genetic testing remains a topic of dispute (77).A positive test result in these women will require bilateral prophylactic mastectomy and bilateral salpingo-oophorectomy, thus the decision needs to be made by a genetic advisory board. Patient being diagnosed with breast cancer at the age of ≤40 years, detection of breast cancer at the age of ≤50 + familial history of breast cancer in first or second degree relatives, history of breast cancer + breast cancer in two or more relatives may indicate genetic testing. Also, due to various known difficulties involved in genetic testing (e.g. risk of mastectomy or oophorectomy, fear of getting cancer, economic reasons, etc.), patients who are at risk for inherited cancer were identified using histopathological type of their tumors (74). A large majority of tumors detected in patients with inherited breast cancer were invasive ductal carcinomas without a special histological type; however, medullary cancers occurred at a higher rate in patients with BRCA-1 gene mutation (77).

Clinical Stage

Clinical staging is based on various imaging procedures and detailed physical examination of breast tissue, skin, and regional lymph nodules (i.e. axillary,

supraclavicular, infraclavicular and internal mammarian).Physical examination should cover an evaluation of tumor diameter, tumor interaction with breast skin (i.e. erythema, edema, induration, traction, etc.), thoracic wall invasion, and regional lymphatic involvement (i.e. palpable nodule, packed or fixed nodule). Physical examination is supported by mammography, ultrasonography, and MRI, where appropriate. Looking at clinical stages of patients in our registry, we find that the percentage of DCIS tumors were 5%, and Stage I breast cancers 26% (see Table 15). In developed countries, the percentage of DCIS tumors are 15 to 20%, while Stage I breast cancers are close to one half of total invasive breast cancers (81,82). A study found that Stage I breast cancers were 62% in the US, and 47% in Germany (81). As discussed earlier, the difference stems from absence of organized, community-based mammographic screens in Turkey. The bulk of our patients are concentrated at Stage II (53%), which is lower in the US (37%), but comparable in Germany (53%). The percentage of patients with locally advanced breast cancer (Stage III) was 15%, which is around 5% in countries where mammographic screens are implemented (16-17).

Diagnosis of breast cancer is usually delayed in younger patients, due to breast density, high tumor proliferation rate, and other factors. These patients had larger tumor size, higher histological grade, lower rate of ER/PR positives, and higher regional lymphatic involvement, compared to older patients (82), and consequently, the mortality rates were higher in this group. In patients aged <40 years registered in our database, the percentage of Stage I breast cancers was 21%, compared to 25% in the 40-49 age group, and 29% in the 50-59 group. Clinical stage III breast cancers are most frequent in patients aged less than 40 years (19%), and decline to 13% in the 60-69 age group (see Table 13). Although the incidence of Stage III breast cancer declined with increasing age, it rises back again at the age of ≤70. In the later age group, reduced awareness due to aging and other diseases may be a factor in this increase.

Clinical stage was more advanced in premenopausal women than menopausal ones (83). The main reason is late detection due to higher breast density. 4.5% of premenopausal women registered in our database had clinical stage I breast cancer, compared to 27.2% with menopausal patients. The rate of locally advanced breast cancer was, however, higher in premenopausal patients (16% vs. 13.6%) (see Table 16).

Pathological Tumor Diameter

The clinical tumor diameter indicates the tumor size determined by physical examination and various imaging techniques. Pathological tumor diameter is, however, the diameter of an invasive tumor as measured on a final pathological specimen. Measurement of pathological tumor diameter, used for treating and monitoring patients with breast cancer, is particularly important among other prognostic factors in that it is easy to perform, standardized and low-cost (87).

In multifocal or multicentric cancers, the diameter of the largest tumor is considered the pathological diameter. Tumor diameter has always ranked in the top three among other standardized prognostic indicators used for breast cancer, such as axillary lymph node involvement, histological grade and age (84-87). It is considered a strong prognostic factor for remote metastasis, particularly in patients without lymphatic involvement. The main hypotheses used to explain this are that tumors of similar sizes will exhibit similar levels of metastasis, and that overall survival is usually better in smaller-diameter tumors, than larger ones (87). In line with these hypotheses, we found that 10-year survival rate in axillary negative (pN0) tumors of sizes between 2 and 5 cm (pT2) and in tumors of sizes ≤1 cm was 66% and 79%, respectively (88-89). In countries where mammographic screens are implemented and breast cancer awareness is high,

the mean pathological tumor diameter is around 10 mm, and the percentage of non-palpable breast cancers is approximately 50%. In patients registered in our database, pathological tumor diameters varied in the range of 1 mm to 20 cm, with a mean tumor diameter of 25 mm (see Table 17). Smaller tumor sizes may be achieved through increased breast cancer awareness through education and broader use of community-based mammographic screens.

Higher breast density, higher tumor proliferative indicators and absence of screens cause tumor diameter at diagnosis to be above average in younger patients (35,54-55). In patients registered in our database, the mean tumor diameter was 25 mm, and 28 mm in patients aged <40 years, and 24 mm in the 50-69 age group. Tumor diameters were ≤1 cm in 9.5%, between 1 and 2 cm in 38.5%, between 2 and 5 cm in 46%, and >5 cm in the remaining 6% of the patients (see Table 18). Pathological T1 rates were 43% in the <40 age group, and 50% in the ≥40 age group. These results indicate that tumors are detected late in younger patients.

Pathological tumor diameter was larger in premenopausal women then menopausal ones, factors for which similarly include higher breast density and faster tumor proliferation. Percentage of pathological T1 (pT1) tumors was 47% in premenopausal patients, and 49% in menopausal ones, which was not statistically significant.

Axillary involvement rate increases with larger pathological tumor diameter in a linear relationship. A study by Nemoto et al. found (90) the following pN0 rates by tumor diameter: 75% in tumors of diameter 0.6 – 1.0 cm, 66% in tumors 1.1 – 2.0 cm, 50% in tumors 3.1 – 4.0 cm, and 35.5% in tumors >5 cm. In our database, percentage of pN0s in patients with pT1, 2 and 3 tumors were 61%, 42% and 18%, respectively (see Tables 26, 27).

Patients diagnosed with invasive ductal carcinoma are known to have poorer prognosis (62). However, in our database, the situation is different in terms of pathological tumor diameter: percentage of pT1-2s is 95% in patients with IDC, and 92% in those with ILC+IMC. A linear relationship exists between tumor diameter and histological grade (HG), i.e. histological grade increases with increasing tumor diameter. Percentage of HG IIIs was 44% in patients with pT1 tumors, and 61% in those with pT3 ones.

Some studies investigating the relationship between tumor diameter and hormone receptors found that pathological tumor diameter was inversely proportional to hormone receptor expression of tumor cells, i.e. estrogen receptor expression weakens in cells constituting the tumor with increasing tumor diameter (91-95). Looking at patients registered in our database, we find that hormone receptor positive ratio decreases with increasing tumor diameter. Percentage of positives for at least one of the hormone receptors was 79% in tumors ≤2 cm, compared to 73% and 68% in pT2 and pT3 tumors, respectively (see Table 43).

A few studies investigating the relationship between pathological tumor diameter and HER-2 expression has reported that the rate of HER-2 positives usually increased with increasing tumor diameter (96-99). A clinical trial has found that HER-2 level in the serum and tumor tissue was directly proportional to tumor diameter (96). According to a univariate analysis performed during the study, the highness of serum HER-2 level was associated with tumor diameter being 2 cm or larger (≥2 cm), age (≥35), postmenopausal status, stage III breast cancer, lymph node involvement and estrogen/progesterone receptor being negative. A multivariate analysis, however, found that disease-free survival decreased with increasing serum HER-2. A study investigating overall survival and disease-free survival, and associated clinico-pathological factors (e.g. age,

receptor status, histological grade, systemic treatment, etc.) in patients with a small tumor diameter (pT≤1 cm) without axillary involvement found that only HER-2 being positive was associated with shorter disease-free survival (97). A Pakistani study also showed an increasingrate of HER-2 positives, and decreasing rate of estrogen and progesterone positives with increasing tumor diameter (98). Another clinical studyidentified tumor diameter, younger age, axillary involvement, HER-2 expression being positive, and estrogen and progesterone expressions being negative as factors affecting early recurrence after adjuvant chemotherapy in high risk group, and did not find a relationship between small tumor diameter and shorter survival (99). However, all factors other than tumor diameter, including positive HER-2, were found to be associated with shorter survival. Our study partially supports the above findings. Rate of HER-2 positives was 21.5% in pT1 cancers, and 25% in pT2 cancers (see Table 45).

A study comparing patients diagnosed with breast cancer during screening and symptomatic breast cancer patients found that tumor diameters were smaller and percentage of breast cancers of subtype Luminal A were higher in the group diagnosed with breast cancer during screening (100). In another study analyzing molecular subtypes, patients with breast cancer subtype Luminal A were compared with HER-2 positive patients (Luminal B and HER-2 positive), and tumor diameters were smaller, and multifocality, node involvement and lymphovascular invasion was lower in the group with Luminal A (101). In another study comparing molecular subtypes of 1214 patients, mean tumor diameters were 19.6 mm in the group Luminal A and B, 22.6 mm in the group HER-2 positive, and 26 mm in the TN group, and the differences were statistically significant (102). In the same study, percentage of pT1 tumors was 66% in the group Luminal A, 58% in Luminal B, 48% in TNG, and 34% in HER-2 positive. These findings show that tumor diameter at diagnosis is far smaller in patients with Luminal A, who have better prognosis due to this and other clinico-pathological properties. Percentages of pT1 tumors by group of patients registered in our database were 51% for Luminal A, 50% for Luminal B, 41% for TNG, and 37.5% for HER-2. Although the ranking did not change compared to the previous study, the pT1 rates in Luminal A and B were close, and it was lower in TNG, and comparable in the TNG. Rate of Luminal A and B breast cancers decreased, and HER-2 and triple negative ones increased with increasing tumor diameter (see Table 55). In pT1 cancers, the percentages of Luminal A, B, HER-2 and TNG subtypes were 66%, 15%, 6% and 12%, respectively, compared to 55%, 9%, 11% and 25%, respectively, in pT3 cancers, representing about a 100% higher ratio of HER-2 and TNG subtypes in pT3 cancers. These findings are consistent with the findings of other studies which suggest better prognosis for patients with smaller tumor diameters.

Pathological Lymphatic Stage

Pathological status of regional lymph nodules are the foremost prognostic factor for breast cancer. The number of metastatic lymph nodules are directly correlated with local recurrence and survival. Patients with lymphatic involvement have 4 to 8-fold higher mortality rates compared to node negative ones (103). Prognosis becomes worse with increasing number of metastatic lymph nodules. Patients with ≥ metastatic lymph nodules have a 70% higher mortality rate than patients with 1 to 3 metastases (103). In a study, 5-year disease free survival was 80% in patients without lymph nodule involvement, and disease-free survival over 5 years of follow-up could be achieved in only 20% of patients with 16 or a higher number of lymph node involvement (104).

Broader use of screening programs and increased awareness levels drive smaller tumor diameter and fewer regional lymphatic involvements in breast cancer

patients, enabling an up to 60% probability of non-palpable breast cancer and not having regional lymphatic involvement (105). In Turkey, absence of community-based mammographic screens and lack of awareness cause these levels to remain low. Thus, our patients differ from those in developed countries in that approximately one half (49.8%) have axillary metastasis at diagnosis (see Table 7). In India, the ratio of regional lymphatic involvement at diagnosis is 64.7% (106).

In a study investigating tumor characteristics and clinical outcomes of invasive breast cancer in 50,399 patients (101), 89.6% of patients were diagnosed with IDC, and 8.2% (4,140 patients) with ILC. In patients diagnosed with invasive lobular cancer, tumor diameters were larger, patients were older, and the percentage of ER/PR positives and HER-2 negatives were higher. No difference was identified between these two histological types in terms of axillary involvement (pN0 rates were 57% and 58%, respectively). Patients also had comparable 5-year disease-free survival rates (85.7% vs. 83.5%). In patients registered in our database, percentages of axillary involvement by histological type were somewhat different from the findings cited above. Pathological regional lymphatic involvement was not detected (pN0) in 52% of patients diagnosed with invasive ductal carcinoma, and in 41% of those diagnosed with ILC+MC. This finding suggests that tumors in patients with ILC+IMC histology are more aggressive, and more proliferative toward regional lymph nodes.

It is known that clinical outcomes in younger women (<40 years of age) are worse than those in older women (55,58-59). These patients exhibit larger tumor diameters and high rates of axillary involvement, lymphatic vascular invasion and hormone receptor negatives, and have higher grades, higher proliferation and S-phase fraction. In patients registered in our database, axillary involvement rates also significantly decrease with increasing age. Percentage of pN0s was 43.6% in women aged less than 40 years, 52% in the 50-59 age group, and as high as 55.6% in >70 age group (see Table 19). Comparing pN0 rates in patients aged less than 40 years with patients aged ≥40 years, we find that axillary involvement rate is lower in the older age group (43.6% vs. 51.4%, see Table 20). As can be seen in this table, rates of pathological N1, 2 and 3 were similarly higher in the below 40 group, than other age groups. The percentage of pN2 was 18% in the <40 age group, 12.7% in the 60-69 age group, and around 14% in the ≥40 age group.

Similar to younger patients, premenopausal patients also had larger tumor diameters, higher rates of axillary involvement, and poorer prognoses (107). Also in our database, the frequency of axillary lymph node involvement was higher in premenopausal patients, compared to menopausal ones. The rate of pN0 was 47%, pN1 30%, and pN2 16% in premenopausal patients, compared to 53%, 27%, and 14%, respectively, in menopausal ones (see Table 21). Percentages were similar when pN0 rate was compared with pN1-3 rates based on menopausal status (see Table 22).

The rate of regional lymphatic involvement increased with larger tumor diameter, a key prognostic factor (108). In a study showing that tumor diameter determined prognosis independent from lymph node involvement, comparing patients without axillary involvement and tumor diameter <1 cm with patients with tumor size between 2 and 5 cm, there was a small difference, i.e. 79% vs. 66%, favoring smaller tumor size (109). As discussed above, our patients also had an increasing rate of lymphatic involvement with larger tumor diameter. Pathological N0 rate declined to 18% in patients with pT>5 cm, from 61.5% in patients with pT ≤2 cm (see Table 23,24). The results were similar with pN2 and pN3 rates. pN2 and pN3 rates, 10% and 3.6%, respectively in pT1 tumors, were

17.9% and 8.4% in pT2 and pT3 tumors, respectively, increasing to 31.7% and 23.6%, respectively, in pT3 tumors.

Rate of regional involvement increased and prognosis became worse with increasing histological grade. Although dependent on other prognostic factors, 10-year survival was 90 to 94% at lower histological grades, declining to 30 to 75% in patients with higher histological grades (89-109). 70% of patients with histological grade (HG) I were axillary involvement negative, compared to 52% in patients with HG II, and 42% with HG III (see Tables 31 and 32). Similarly, 2.3% of patients who were HG I, and 4.9% and 9.1% of those who were HG II and III, respectively, were pN3.

Histological Grade

The most common histological grading (HG) systems used for breast cancer are Scarff-Bloom-Richardson, Fisher's nuclear grading, and Nottingham Combined Histological Grading (HCG) (89). Nottingham Grading System (NGS), being the Nottingham (Elston-Ellis) modification of the Scarff-Bloom-Richardson grading system, is currently used and recommended by World Health Organization, American Joint Committee on Cancer (AJCC), the European Union (EU), and the Royal College of Pathologists (108). Breast Unit at Istanbul Medical School also uses a modified version of the Scarff-Bloom-Richardson system for histological grading of breast cancer. Studies usually associate higher grades with younger age (<40), high local recurrence, increased axillary involvement, larger tumor diameter, and low survival duration (110-115). Considering other prognostic factors such as tumor diameter and axillary involvement, 10-year overall survival is cited as 90 to 94% in patients with lower grades, and 30 to 78% in those with higher grades (116-117).

Studies comparing properties of breast cancers detected in Caucasian females in developed countries with breast cancer properties in developing countries found that breast cancers occurred at younger age, diagnosed at later age, and had higher histological grade, and triple negative breast cancers were more common in developing countries (4-6,37,118). Kakarala et al. (118) evaluated 360,933 patients diagnosed with breast cancer between years 1988 and 2006 during the cancer program Surveillance Epidemiology and End Results (SEER), conducted by US National Cancer Institute (NCI). Patients of Indian / Pakistani origin were compared with Caucasian and African-American patients based on breast cancer diagnosis age, histological types, hormone receptor status, histological grade and survival. Females of Indian/Pakistani origin were diagnosed with breast cancer at younger ages, had a higher rate of hormone receptor negatives, and had a higher rate of invasive ductal carcinomas and inflammatory carcinomas. No survival difference could be detected between these two races, and African-American females had lower survival rates. The study compared the four races based on histological grade (HG) and found the following HG III ratios by race: 34% in Caucasians, 40% in Hispanics, 42% in Indians/Pakistani, and 49% in African-Americans. As can be seen, higher tumor grades, indicating poor prognosis, were higher in Caucasians than in Asian and African-American breast cancer patients.

Looking at the histological grades of patients registered in the National Breast Cancer Database, we found that 5% were HG I, 45% were HG II, and 50% were HG III. In other words, HGs were as high as those of African-Americans in half of the patients. This high rate did not vary between histological types. Looking at the HG distribution by age, younger patients had higher HGs, similar to literature reports (35,40,41,52,89). Percentage of HG Is was half that in the 60-69 age group, and the percentage of HG IIIs (60%), 16% larger than that in the 60-69 age group (see Table 28). When divided into age groups of <40 years and ≥40

years, 2.6% in the <40 group were HG I and 60% were HG III, compared to 5% and 48%, respectively, in the ≥40 age group (see Table 29).

Some studies have reported higher HG with increasing tumor diameter, indicating a parallelism between tumor diameter and HG (95-119). In patients registered in our database, histological grades were higher with increasing tumor diameter. 7.8% of patients with pathological T1, and only 1.6% with pT2 were HG I, whereas 44% of pT1s, 58% of pT2s and 61% of pT3s were HG III (see Table 30).

We previously discussed that the rate of axillary involvement increased with increasing tumor diameter. A similar relationship exists between tumor histological grade and axillary involvement (120-122). Frequency of axillary involvement in patients registered in our database increased with higher histological grade. Percentage of N0s was 70% in HG I cancers, declining to 52% in HG II and 46% in HG III ones. Pathological axillary involvement rate (pN+) also increased with higher histological grade (HG) (see Tables 31 and 32). 1.4% of all patients with pN3 were HG I, 28% were HG II, and 71% were HG III.

Receptor positive rates increased with higher tumor histological grade. In a clinical study, 95% of patients who were HG I, 90% of those who were HG II and 50% of those who were HG III were ER positive (123). Comparing patients registered in our database in terms of receptor positive rates and HG, we found a similar picture. Percentage of breast cancer patients who were either ER or PR positive was 75.6%, which was 94% in patients who were HG I. Looking at the relationship between the rate of hormone receptor (HoR) positives and HG, we found that the rate of HoRdecreased with higher HG. 85% of the patients were HoR positive and HG II, and 66% were HoR positive and HG III (see Table 42).

We discussed earlier that HER-2 positivity was one of the factors that adversely impacted prognosis. Clinical trials conducted in the West have found a linear relationship between histological grade and HER-2 positivity, with HER-2 positivity increasing statistically significantly with higher HG (124-126). In a clinical trial conducted by Hoff et al. (126), <1% of HG I patients were HER-2 positive, and it was recommended for these patients to repeat FISH or SISH tests in the presence of HER-2 positivity. However, in a Saudi Arabian study, although the number of HER-2 positive patients increased with higher HG, the increase was not statistically significant (127). From a prognostic viewpoint, the linear relationship between HER-2 positivity and high HG was also apparent in our dataset; 2% of HER-2 positive breast cancer patients had HG I, 28% had HG II, and 70% had HG III breast cancers (see Table 48).

Comparing the breast cancer molecular subtypes with cancer histological grade, we found that HGs were higher in the triple negative and HER-2 positive breast cancer groups (120-122,126). In a clinical trial by Spitale et al. (122), HG III rates by molecular subtype were 76% in the TNG, 67% in the HER-2 positive group, 15% in the Luminal A group, and 47.5% in the Luminal B group. Looking at patients registered in our database, we found that 87% of HG I patients were subtype Luminal A, 10% were Luminal B, and 3% were TNG, and the HER-2 positive group had no patients with HG I tumors (see Tables 55-57). Ratios of patients with HG III breast cancer by group were 83.5% in the triple negative group, 82% in the HER-2 positive group, 43% in the Luminal A group, and 61% in the Luminal B group. Although the ranking of HG III ratios was similar to findings of Spitale et al., the ratio of HG IIIs in all our molecular subtypes were higher than the rates seen in developed countries. As mentioned above, these results support our finding that breast cancer has worse prognosis and higher histological grades in developing countries.

Hormone Receptor Expression

Estrogen and progesterone are responsible not only for the development and growth of breast, but also for the growth of a large portion of breast cancer. Estrogen and/or progesterone receptors being positive in breast cancer cells helps with determining not only the prognosis of breast cancer, but also whether the contemplated treatment will be effective (a predictive factor). Studies have shown that positivity rates of hormone receptors in breast cancers detected in developed countries were higher than those in developing countries. In an evaluation of 360,933 patients diagnosed with breast cancer between years 1988 and 2006 under SEER (Surveillance Epidemiology and End Results) Cancer Program run by US National Cancer Institute (NCI), 79% of Caucasians, 72% of Asians (Indian/Pakistani immigrants), and 63% of African-Americans were ER positive (118). A similar difference was apparent for progesterone receptor positivity rates as well, with 68% in Caucasians, 62% in Asians, and 53% in African-Americans. These results indicate that receptor positivity and prognosis were more favorable in Caucasians, suggesting better effectiveness of hormonal therapy. In our patients, 70% were ER positive, and 58% were PR positive, which are lower than those found in Caucasians, closer to those in Asians, and higher than those in African-Americans.

In a study comparing invasive lobular cancer with invasive ductal cancer, ER and PR positivity rates were 93% and 67%, respectively, in patients diagnosed with ILC, and 81% and 60%, respectively, in those with IDC (105), representing a significantly higher receptor positivity ratio in patients diagnosed with ILC, compared to those with IDC. 68% of patients registered in our database who had been diagnosed with invasive ductal carcinoma, and 78% of those diagnosed with ILC+IMC were ER positive, similar to the findings cited above (see Tables 13 and 14).

In breast cancer, younger age (<40 or <35 years of age) infers negative clinical and pathological findings, lower hormone receptors, and, consequently, shorter survival. In most studies, hormone receptor positivity rates were lower in younger women than in older ones (54-60,105). ER positivity ratio was 71% in our patients older than 40 years, which declined by 11 percentage points to 60%in patients younger than 40 years. ER positivity rates were also lower in premenopausal patients, compared to menopausal ones (66% vs. 73%, see Tables 36 and 37).

In general, PR positivity rates were lower than ER positivity rates (118-120). Progesterone positivity rates were lower than ER positivity rates in our patients also, without a meaningful difference between age groups in terms of PR positivity (57% in <40 age group vs. 59% in ≥40 age group; see Table 38). PR rates were slightly higher in premenopausal patients, compared to menopausal ones (61% vs. 58%).

We previously discussed that hormone receptor positivity rates in Caucasians living in developed countries were higher than in developing countries and breast cancer patients of other races. In a study comparing clinico-pathological attributes of breast cancer between races, positivity rate of at least one of the hormone receptors was 79% in Caucasians living in the US, and 76% in our dataset. The positivity frequency of at least one hormone receptor (HoR) in our patients continues to increase with age (71% in <40 age group vs. 72% in >70 age group; see Tables 40 and 41). 75% of premenopausal patients, and 77% of menopausal ones were positive for at least one of the hormone receptors (see Table 42).

In breast cancer patients, prognosis declines and hormone receptor positivity decreases with increased tumor diameter (122,123,128). It has been shown that ER/PR positivity declined similarly with increasing tumor diameter in breast

cancers occurring in BRCA-1 carriers also (129). The same variation was apparent in patients registered in the National Breast Cancer Database, with hormone receptor positivity declining with increasing tumor diameter (79% for T≤2 cm vs. 68% for T>5 cm; see Table 43).

Studies investigating the effects of hormone receptors on axillary involvement yielded variable results. A Pakistani study did not detect any relationship between hormone receptor positivity and lymphatic involvement, whereas other studies found a strong relationship between progesterone receptor negativity and lymphatic involvement (128,130-131). In patients registered in our database, a conflicting relationship was found between the probability of being positive for at least one of the hormone receptors (HoR) and lymphatic involvement. The probability of HoR positivity was 77% in patients without pathological axillary involvement (pN0), 78% in pN1 and 76% in pN2, which were remarkably close, with a significant decline only in pN3 (see Table 41).

In almost all clinical trials, hormone receptor positivity declined with higher histological grade (HG) (117-122). In a study, ER positivity rate in patients with HG I breast cancer was 90%, which declined to 72% and 44% for HG II and HG III, respectively (120). In our patients, HoR positivity similarly declined with higher HG, which was highest between HG I-II and HG III (94% for HG I, 85% for HG II, and 66% for HG III; see Table 42).

HER-2 Expression

10 to 34% of patients with invasive breast cancer are HER-2 receptor positive (proto-oncogene), and HER-2 is an important prognostic and predictive factor (126). HER-2 positivity indicates negative prognosis. Because the risk of local and/or systemic recurrence is high, adjuvant chemotherapy and trastuzumab areroutinely recommended in these patients when the tumor size exceeds 1 cm (even if they are hormone receptor positive) (124-127,132). Adjuvant chemotherapy and trastuzumab are also indicated when tumor size is >0.5 cm, when the patient is hormone receptor negative (133). OncotypeDx and MammaPrint tests are useful in determining which HER-2 positive patients to monitor without chemotherapy (124-128,132-133).

HER-2 positivity rate in patients registered in our database was 22.7%. Reported HER-2 positivity rates differ between datasets. A 164-patient dataset from Saudi Arabia reported 35%, while a 401-patient datasetfrom Cleveland Clinic reported 14.2% (126,127). HER-2 positivity rate in patients diagnosed with invasive ductal carcinoma was significantly higher than with invasive lobular cancers (124-133). In a study conducted by Cleveland Clinic Foundation, 15.7% of patients with IDC, 3% of patients with ILC, and 30% of patients with metastatic breast cancer were HER-2 positive (126). The HER-2 positivity rate (24.5%) was significantly higher in our patients diagnosed with IDC, than those with ILC+IMC (14%) (see Table 11).

HER-2 positivity was higher in younger patients (<40 years or <35 years) than older ones (124-128,132-133). In our group of patients aged <40 years, the percentage of patients who were HER-2 positive (26.5%) were significantly higher than in patients aged ≥40 years (22%) (see Table 43). A comparison of premenopausal breast cancer patients with menopausal patients did not reveal any significant difference in terms of HER-2 positivity rates (see Table 44).

HER-2 positivity, tumor diameter, high histological grade, and hormone receptor negativity are considered important negative prognostic factors. Studies have reported conflicting results on the potential relationship between HER-2 positivity and tumor diameter (79,85,95,111,112,121-132). In our patients with known HER-2 receptor status, a regular relationship was not found between tumor

diameter and HER-2 positivity (see Table 45). HER-2 positivity, 21.5% in patients with a tumor diameter ≤2 cm, increased to patients with pT2, and declined back to 20.2% in those with pT3 tumors.

Axillary involvement currently remains as the foremost prognostic factor. Regional metastasis or increasing number of lymph nodules with metastasis are indicative of poor prognosis. Like axillary involvement, HER-2 positivity also indicates poor prognosis. In our patients, the HER-2 positivity rate was higher in those with axillary involvement, and HER-2 positivity increased with increasing axillary involvement positivity (N2,3) (see Table 46). HER-2 positivity rate was 19.6% in patients negative for axillary metastasis, 23.8% in patients with pN1, 28.1% with pN2, and 34% with pN3. These differences were statistically quite significant, showing a very high probability of regional lymph nodule involvement in patients positive for HER-2. Patients were divided into two groups of pN0 and pN1-3, and HER-2 positivity rate was significantly higher in the axillary-positive group (19.6% vs. 26.5%; see Table 47).

In a study comparing HER-2 receptor positivity with histological grade (HG) in invasive breast cancer patients, 1% of patients with HG I invasive ductal carcinoma were HER-2 positive, compared to 17% and 23% with those with HG II and HG III, respectively (126). In other words, this study has very clearly shown that HER-2 positivity increased with higher histological grade. In our study, HER-2 positivity similarly increased with higher HG. HER-2 positivity rates were 10% in patients with HG I, 15.4% in those with HG II, and 28.2% in those with HG III, representing a very clear and significant increase (see Table 48).

Molecular Subtypes

Tumor diameter, lymph nodule involvement, and hormone receptor and HER-2 (human epidermal growth factor receptor) positivity are traditionally used to help determine prognosis and treatment in breast cancer. These prognostic and predictive factors are rough indicators, and a large number of patients receive over- or under-treatment. Consequently, breast cancers with similar histopathological properties exhibit different clinical properties, follow different courses, and patients respond differently to therapy. These differences may be mainly associated with limitations of the current, morphology-based classification of breast cancer.

Expression properties of genes and their phenotypical differences highlight the heterogenic nature of breast cancer as a disease, and enable its classification at molecular level. And the number of molecular subtypes is growing steadily (102).

Originally, Perou et al. (134) identified four different molecular subtypes of breast cancer: estrogen receptor positive / luminal-like, basal-like (triple negative), HER-2 positive and normal breast. Later, the group luminal-like was further divided into two groups of Luminal A and Luminal B, which are the most frequent subtypes of breast cancer. These tumors express estrogen and progesterone receptors, genes related to ER activation (LIV1, GATA3 and cyclin D1), and Luminal cytokeratins (134-137). They are frequently low grade, and contain less than 20% TP53 mutation. Luminal A tumors usually contain high ER and genes associated with ER. Their gene expression related to HER-2 and proliferation (like Ki67) is low, and they have the best prognosis. Luminal B tumors, however, have high proliferation and TP53 mutation tendency. Their ER and ER gene expression is lower, and they come after Luminal A in terms of prognosis.

Ratios of molecular subtypes in patients with breast cancer vary between countries (136). In a Dutch study with 295 patients, 41.7% of patients were Luminal A, 18.6% were Luminal B, 11.9% were HER-2+, 18% were TN (basal-

like), and 9.8% were normal breast (138). Because this classification included five groups, the percentage of Luminal A was low, and with the normal breast added, Luminal A will exceed 50%. In a similar Swiss study, molecular subtypes were 73.2% Luminal A, 13.8% Luminal B, 5.6% HER-2+, and 7.4% TN (102). In a Korean study, 39% of patients were Luminal A, 17.4% were Luminal B, 18.5% were HER-2+, and 14.6% were triple negative (139). In our database, 62.5% of patients had Luminal A, 15% had Luminal B, 8.5% had HER-2 positive, and 14.6% had triple negative breast cancers (see Table 49). Of note, the percentage of triple negatives in our dataset was twice as high compared to Swiss triple negatives, and half that of Korean patients. This finding supports the proposition that the percentage of triple negative breast cancers is higher in developing countries, and that rates in Turkey are somewhere in between.

Studies have shown that tumor diameters at diagnosis are smaller in Luminal A and B cancers, compared to HER-2 positive and triple negative ones (102,134-137). In a study conducted by Spitale et al. (102), pT1 rates were 62% overall, 65% and 58% in patients with Luminal A and B, respectively, 48% in the triple negative group, and 34% in the HER-2+ group. Data in our database were consistent with the literature, with ratios of Luminal A and B breast cancers decreasing significantly with increasing tumor diameter (Table 53). pT1 rates were 50% in Luminal A and B, 37.5% in the HER-2+ group, and 41% in the triple negative group. The triple negative group having a higher rate of pT1 then the HER-2+ group in this ranking contradicts other studies (102,134-137). However, pT3 rates were 4.8% in Luminal A, 3.3% in Luminal B, 7.4% in HER-2 positive, and 9.3% in the triple negative group, with TNG having the largest number of pT3 tumors.

In a study investigating molecular subtypes, pN0 rate was 60% overall, 62% and 55.5% in groups Luminal A and B, respectively, 50.8% in the HER-2 group, and 57.5 in the triple negative group (102). These results indicate higher axillary involvement particularly in HER-2+ patients, and thus poorer prognosis. Looking at regional lymphatic involvement rates of patients based on molecular subtypes, 64% of all pN0 patients were in the Luminal A group, 13.5% were in the Luminal B group, 6.2% were in the HER-2+ group, and 16% were in the triple negative group (see Table 53). In other words, pN0s were highest in the Luminal A group and lowest in the HER-2+ group, which is consistent with the findings above. AS regards the pN0 rates of patients in each molecular subtype: 55% of Luminal A patients, 49.7% of Luminal B patients, 39.6% of HER-2+ patients, and 59.7% of triple negative patients were pN0, which is indicative that among hormone receptor negative groups, HER-2+ patients had a higher risk of regional proliferation compared to patients in the triple negative group. Looking at the molecular subtype ratios from pN0 toward pN1, pN2 and pN3, we find that the percentage of patients in the Luminal A group decreased [to 48% (pN3) from 64% (pN0)], and that of patients in the HER-2+ group increased [to 18% (pN3) from 6% (pN0)] with increasing axillary involvement rate (see Table 53). A variation similar to that with the HER-2+ group was apparent in the Luminal A group (see Table 53). When we compare pN0 and pN+ (1-3) between molecular subtypes, we find that the percentage of Luminal A and TNG breast cancers decreased, and percentage of Luminal B and HER-2+ cancers increased in the presence of axillary involvement (see Table 54).

Histological grade was lower in the estrogen receptor positive molecular groups, compared to other groups (102,135-140). In the study by Spitale et al. (102), percentage of Luminal A and B patients with HG I and II were 85% and 52.5%, respectively, whereas it was significantly lower in the triple negative group and HER-2+ group (24% vs. 33%). In our database, 87% of patients with HG I breast cancer had Luminal A, and 10% had Luminal B breast cancers (see Table

55). And 50% of patients with HG III tumors were in the Luminal A, and 15% were in the Luminal B group (see Table 55). 7% and 4% of patients in groups Luminal A and B, respectively, had HG I tumors, whereas no patient in the HER-2+ group, and only 1% of patients in the triple negative group had HG I tumors. 43% of Luminal A patients, 61% of Luminal B patients, 82% of HER-2+ patients, and 83.5% of triple negative patients had poor histological grade (HG III). A comparison of HG I vs. HG II+III tumors in molecular subtypes yielded a similar result (see Table 56). However, when we compare HG I+II values of molecular subtypes with HG III ones in two separate groups, we find the following distribution of HG I+II rates across molecular subtypes: 57% in Luminal A, 39% in Luminal B, 18% in HER-2+, and 16% in triple negative group (see Table 57). Here, we also note that the ranking did not change, Luminal A had the most favorable molecular subtype, followed by Luminal B, and hormone receptor negative molecular subtypes had poor histological grades.

The percentage of TN breast cancers is particularly high in premenopausal women (102,140). In a study, 37% of TN breast cancers were detected in premenopausal women, and 13% of HER-2+ patients, and 23% of Luminal A ones were premenopausal (102). In another study, the percentage of TN breast cancers in premenopausal US women was 14.5%, which was nearly twice as high in African-American premenopausal women (27.2%) (140), compared to 9.3% and 16%, respectively, in menopausal ones. These results indicate a higher rate of TN breast cancers (twice as high) in premenopausal women versus menopausal ones, and in African-American women versus Caucasian ones. In our study, looking at molecular subtypes in premenopausal versus menopausal women, there was no significant difference between Luminal A, B and HER-2+ groups, whereas triple negative breast cancer rate was 16.3% in premenopausal women, compared to 13.2% in menopausal ones (see Table 51).

In a US study investigating molecular subtypes in 1274 patients, 24% of patients with TNG cancers were <40 years of age, but only 11% of those in the Luminal A group were below 40 (140). Also, in a European study 11% of triple negative patients were <40 years of age, compared to 3.2% and 7.7% of Luminal A and B patients, respectively, and 4.4% of HER-2+ patients (102). As can be seen, percentage of younger patients in the TNG was significantly higher compared to other groups. Looking at patients in our database, we see a higher rate of, in particular, early age breast cancers, and consequently our early age (<40 years) breast cancer rates in all molecular subtypes were higher compared to developed countries (see Table 49). 20% of patients in the triple negative group were <40,and 15% of those in the Luminal A group were at a younger age. 14% of patients in the Luminal A group were at an older age (≥70 years), compared to 6% of triple negative ones. 56% of our patients aged less than 40 years were in the Luminal A group, which increased with age, and 70% of breast cancer patients aged ≥70 were in the Luminal A group (see Table 49). This relationship exhibits an opposite picture with those in Luminal B and TNG, where the percentage of patients in these subtypes decline with increasing age (see Table 49). When we compare patients in two age groups of <40 and ≥40, we find that 56% of patients in the <40 age group, and 64% of patients in the ≥40 age group had Luminal A cancers (see Table 50). Subgroups Luminal B and triple negative, however, exhibit an opposite picture: 18.5% and 17.4% for Luminal B and triple negative respectively, in the <40 age group declined to 13.8% and 14%, respectively, in the ≥40 age group, but there was no age-related change in the HER-2+ group (see Table 50).

Hormone receptor negative molecular subtypes were HER2+/ER- and TN cancers. The breast cancer group HER2+/ER- have high HER-2 and HER-2 gene expression, and low or negative Luminal hormone-related gene expression

(≤10%) (135-140). They have a high proliferation rate, 75% are high grade, and more than 40% contain p53 gene mutation. These account for 5 to 10% of all breast cancers. Before introduction of trastuzumab, patients in this group used to be considered poor prognosis. But with the addition of trastuzumab in the treatment regimen, serious increases in mean and disease-free survival durations were observed at full response to therapy. In our study, 8.5% of all patients were in the HER-2+/ER- group. 8.4% of patients aged <40, 7% of those in the 40-49 age group, 10.4% of those in the 50-59 age group, 9.4% of those in the 60-69 age group, and 7.5% of those in the ≥70 age group were in this group (see Table 49). When we evaluate this group based on 40 years of age, there was no difference between age groups <40 years and ≥40 years (see Table 50). Based on menopausal status, 7.3% of premenopausal patients, and 9.6% of menopausal patients were in this group (see Table 51).

Large tumor diameter at diagnosis and extended axillary involvement indicates poor prognosis in the HER-2+/ER- group (135-141). In our database, larger tumor diameter similarly increased the number of patients in the HER2+/ER- group (see Table 52). 6.4% of T1 tumors (≤2 cm), 10% of T2s, and 11.2% of T3s were in this group. Similarly, a parallelism was found between pathological axillary involvement and the number of patients in this group (see Table 53). Percentage of pN0 patients in this group was 6.2%; the percentage pN3 patients was nearly three times as high (18.1%). A comparison of pN0 with other pN1-3 yielded a similar picture (6.2% - 10.9%; see Table 54). None of the Histological Grade (HG) I patients, and 3.9% of HG II patients, and 13.2% of HG III patients were in this group (see Table 55).Percentage of HG II+III patients in this group was 9.2%, HG I+II 3.4%, and HG III 13.2% (see Table 56).

In breast cancers of molecular subtype triple negative (basal-like), hormone receptor and HER-2 gene expressions are very low, and proliferative gene expressions (basal gene cluster: basal epithelial cytokeratins, epidermal growth factor receptor, c-kit, vimentin, p cadherin, etc.) are high (135-137). Approximately 80% of breast cancers occurring in carriers of BRCA1 mutation are triple negative breast cancers (140). This molecular subtype is more common among women in younger age groups (<40 years), premenopausal and Asian/African (135-140). The percentage of patients in this group varies in the range of 7 to 30%, and they have poorer prognosis (102,135-139). In our database, 14.6% of patients were in the TNG, representing a lower rate than in Asians and Africans, but higher than in some developed countries (102,135-143).

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