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Use of hormone replacement therapy for increasing breast cancer incidence rates

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Abstract
Cancer is a group of abnormal cells formed by cells that grow continuously, are unlimited, and are not coordinated with the surrounding tissue and physiological functioning. Cancer occurs due to the rise and breeding of the surrounding tissue (infiltrate) while destroying (destructive), can spread to the other part of the body, and is generally fatal if left unchecked. Menopause is a condition that all women will pass. Some symptoms will appear when in that condition. Therefore many women use hormone replacement therapy to relieve symptoms of menopause. Breast cancer is a very common problem in the community; if the problem is not quickly overcome, breast cancer can cause death. Therefore, this study aimed to explore the effect of hormone replacement therapy (1) an increased incidence of breast cancer. The results of the comparison between the three journals stated that after a decline in the use of hormone replacement therapy, breast cancer incidence rates decreased, so it is concluded that when the use of hormone replacement therapy is excessive over five years, it may be a risk factor of breast cancer.

Keywords: hormone replacement therapy, breast cancer, menopause

Introduction

Cancer is a collection of abnormal cells formed by cells that grow continuously, are not limited, are not coordinated with the surrounding tissue, and do not function physiologically. Cancer occurs because the surrounding tissue arises and multiplies (infiltrative) while damaging it (destructive), can spread to other body parts, and is generally fatal if left unchecked. [1; 2] Cancer is one of the leading causes of death worldwide. In 2012, around 8.2 million deaths were caused by cancer. Lung, liver, stomach, colorectal, and breast cancer are the biggest causes of cancer deaths yearly. The highest cancer in Indonesia is breast cancer. Breast cancer is the most common cancer in women, which accounts for 18% of all cancers in women. Every year 1 million new cases of breast cancer are found worldwide. [3; 4]

Some factors that increase the risk of breast cancer are old age, early menarche (age of first menstruation), older age at menopause, older age at first birth, having never been pregnant, family history of breast cancer (especially mother or sister), a history of having suffered from benign breast tumors, consuming hormonal contraceptive drugs in the long term, consuming alcohol and radiation exposure to the breast, especially during the breast formation period [5]. Several literatures reviews state that hormonal use, obesity, alcohol consumption, first pregnancy at old age, and fat intake, especially saturated fat, are associated with an increased risk of breast cancer [6]. Even though the research results state that hormonal use is one of the causes of breast cancer, many women still use it. Therefore, researchers want to know whether Indonesian women, especially women who use hormonal therapy based on research from several journals, find out the bad effects of hormonal therapy as a risk factor for breast cancer. Menopause is a condition that all women will go through. Several symptoms will appear during this condition. Therefore, many women use hormone replacement therapy as a therapy to reduce the symptoms of menopause. Breast cancer is a common problem in society; if breast cancer is not treated quickly, it can cause death. Therefore, this literature study is intended to explore the effect of hormone replacement therapy on the increased incidence of breast cancer. This research aims to inform how much effect hormone replacement therapy has on breast cancer and the dangers that can be caused by hormone replacement therapy.

Literature review

Menopause is the permanent cessation of menstruation due to the ovarian follicles not working. So to determine the onset is done retrospectively, starting from spontaneous amenorrhoea until 12 months later [7]. Menopause is an ovarian failure characterized by the absence of ovarian estrogen, progesterone, and androgens [8]. Terms that are often used to divide the climacteric period:

1. Premenopausal: <2 months before last menstruation
2. Perimenopausal: 2-12 months since last menstruation. Is the time with irregular menstrual cycles before amenorrhea occurs, it may or may not occur. Some experts say the term perimenopause includes women aged 45-65.
3. Postmenopausal: >12 months since last menstruation. [9, 10, 11]

The literature states that the climacteric period lasts for 30 years (age 35-65 years), and is divided into three parts for clinical purposes, namely: early climacteric (35-45 years), perimenopause (46-55 years) and late climacteric (56 -65 years). [12] Women will start to feel various complaints when they don't get menstruation anymore due to a lack of estrogen. It should also be noted that there are around 30% of women, even though they have regular menstruation, have started to feel complaints like menopausal women as a

result of reduced levels of the hormone estrogen in the body. Complaints that occur in premenopausal, menopausal, and post-menopausal women are generally caused by low or lack of the hormone estrogen, although it should also be remembered that other diseases can also cause some of the same complaints. [13] Complaints that arise can be divided into short-term complaints and long-term complaints. Short-term complaints can appear once the menstrual cycle becomes irregular, but most only appear when the woman has not menstruated after six months or more, while long-term complaints will only appear or be seen after approximately ten post-menopausal years. Complaints in perimenopausal women arise as a result of a natural process of aging. The aging process causes the degeneration of body cells, including the ovarian organs. The decreased ovarian function causes a decrease in the production of sex hormones, namely estrogen and progesterone. This degeneration process causes a decrease in the immune system and cell function, affecting the cyclic activity system to the hypothalamus and pituitary. [14] Decreased function of the hypothalamus and pituitary affects the work of the parasympathetic nervous system and the central nervous system, which in turn causes disturbances in the neuro vegetative, neurophysiological, neuromotor, and metabolic systems that clinically appear as symptoms of perimenopause.

Reduced or lost estrogen can lead to vasomotor symptoms, sleep disturbances, mood disturbances, depression, urinary tract and vaginal atrophy, and an increased risk of chronic disorders such as osteoporosis, cardiovascular disease, and cognitive decline. Vasomotor symptoms are the most frequently reported complaints by patients. The basis for these pathophysiological changes is related to estrogen deficiency, the mechanism of which is widely known. Two types of breast cancer symptoms are vasomotor disturbances and urogenital complaints. [15]

Breasts in men and women are the same until puberty (11-13 years) because estrogen and other hormones affect breast development in women. In women, breast development is active, whereas in men, the mammary glands and ducts are underdeveloped, and the sinuses are incompletely developed. Breasts sensitive to hormonal influences cause breasts to experience neoplastic growth, both benign and malignant. [16]

Breasts are part of the reproductive organs whose main function is to secrete milk for baby nutrition. The breast consists of ductal tissue, fibrous that binds the lobes, and fatty tissue within and between the lobes. 85% of breast tissue is made up of fat. Slightly below the center of the mature breast is the nipple (mammary papilla), a pigmented protuberance surrounded by the areola. The nipples and areolas are usually a different color and texture than the skin around them. The color varies from pale pink to black and dark during pregnancy and lactation. The nipple usually protrudes from the surface of the breast.

Breast cancer can occur anywhere within the breast, but the majority occurs in the outer upper quadrant, where most breast tissue is located. In determining the location of breast cancer, the breast is divided into four quadrants: the lateral quadrant (upper edge), lower lateral, medial (top center), and lower median. The spaces around the lobules and ducts are filled with fat, ligaments, and connective tissue. The amount of fat in a woman's breasts largely determines their size. The actual milk-producing structure is almost the same in all women. Female breast tissue is sensitive to cyclic changes in hormone levels. Younger women may have denser breast tissue and less fatty tissue than older women who have gone through menopause.

After knowing the abovementioned complaints, the question arises of how a menopausal/post-menopausal woman deals with these complaints. Because a lack of the hormone estrogen causes health problems in menopausal/post-menopausal women, the treatment is by administering estrogen replacement hormones, known as Estrogen Replacement Therapy (ERT). Because the administration of estrogen is usually combined with the administration of the hormone progesterone, it is known as Hormone Replacement Therapy, Hormone Replacement Therapy (HRT), or Hormone Replacement Therapy (HRT). Menopause is a normal and natural event that every woman must experience, and its occurrence cannot be prevented at all, and the administration of hormone replacement therapy is not intended to prevent menopause. However, it only intends to prevent the health effects of menopause, both short-term and long-term complaints.

HRT is defined as a) Therapy using the given hormone to reduce the effects of hormone deficiency; b) Administering hormones (estrogen, progesterone, or both) to postmenopausal women or women whose ovaries have been removed, to replace estrogen production by the ovaries; and c) Therapy using estrogen or estrogen and progesterone given to postmenopausal women, or women who have undergone ovariectomy, to prevent the pathological effects of decreased estrogen production. [17]

The use of hormone replacement in Indonesia is still very limited. In contrast to Western countries, there are fewer complaints and people's acceptance of menopause; educational, social, and economic factors affect the amount of hormone replacement use in Indonesia in particular and Asian countries in general.

Breast cancer (Carcinoma mammae) is a malignant neoplasm disease from the parenchyma. Breast cancer by WHO is included in the International Classification of Diseases (ICD) with code number 174 for women and 175 for men. Cancer is one of the main causes of death worldwide. In 2012, around 8.2 million deaths were caused by cancer. Lung, liver, stomach, colorectal, and breast cancer are the biggest causes of cancer deaths yearly. [18]

According to Globocan (IARC), in 2012, it is known that breast cancer is cancer with the highest percentage of new cases (after controlling for age). Namely, 43.3%, and the percentage of deaths (after controlling for age) due to breast cancer was 12.9%. Lung cancer is not only a type of cancer with the highest new cases and the main cause of death from cancer in the male population, but lung cancer also has a fairly high percentage of new cases in the female population, which is 13.6% and deaths from lung cancer are 11.1%. The Globocan data shows that new cases and deaths from liver cancer in the male and female population have an almost equal percentage, while breast cancer and prostate cancer have a much lower percentage of deaths compared to the percentage of new cases, so if cancer can be If detected and treated early, the chances of recovery will be higher. [19]

Based on the picture above, it is known that the most common cancers at Dharmais Cancer Hospital for four consecutive years were breast, cervical, lung, ovarian, rectum, thyroid, colon, hepatoma, and nasopharynx cancers. Non-Hodgkin's lymphoma cancer was the 10th most common cancer in 2010 and 2011, but in 2012 and 2013, the 10th most common cancer was soft tissue cancer. During 2010-2013, breast, cervical, and lung cancer were the three most common diseases at Dharmais Cancer Hospital, and the number of new cases and deaths from these cancers continued to increase. [20] According to Hanahan and Weinberg, six fundamental physiological changes together allow the growth and development of malignant cells the following changes: a) Independent in terms of growth signals; b) Not sensitive to inhibitory growth signals (anti-growth); c) Able to avoid apoptosis (programmed cell death); d) Unlimited replication capability; e) Continuous angiogenesis capability; and f) Able to infiltrate into other tissues and metastasize. [21]

Breast cancer is the highest type affecting Indonesian women, with a prevalence rate of 26 per 100,000 women (RI Ministry of Health 2010). There are different types of breast cancer, with about 70 percent being tumors sensitive to the female hormone estrogen. Breast cancer is often called ER+ (estrogen receptor positive) breast cancer. Breast cancer is most common in postmenopausal women when the ovaries (ovaries) no longer produce estrogen. After menopause, the body will produce estrogen in fat tissue and breasts. Endocrine therapy is a type of treatment that stops the production or action of estrogen on tumor cells. As mentioned above, breast cancer is most common in postmenopausal women, and most of these cancers are ER+. Breast tissue contains fat cells; these fat cells produce an enzyme called aromatase, which produces estrogen. In normal breast tissue, aromatase levels are still under control. [22]

The older a woman is, the more fat cells in her breasts tend to produce large amounts of the aromatase enzyme, increasing local estrogen levels. This locally produced estrogen is believed to play a role in triggering breast cancer in postmenopausal women. Once formed, the tumor increases estrogen levels to help it grow. Clusters of immune cells in tumors also appear to increase estrogen production. Recent studies have also identified a link between obesity and estrogen production. Data shows that obesity increases the risk of breast cancer two times in older women. [23]

According to Moningkey and Kodim, the specific causes of breast cancer are still unknown. However, many factors are thought to influence the occurrence of breast cancer, including reproductive factors, hormone use, fibrocystic disease, obesity, fat consumption, radiation, family history, and genetic factors. [24]

Based on the principle of benefit and ease of working in the clinic as well as energy and cost efficiency, the discussion of solid tumor diagnostics is then focused on: clinical examination, laboratory examination, examination of anatomical pathology, other supporting examinations, staging of solid tumors, procedures for writing solid diagnosis tumors and the patient's performance status. In other investigations, there are imaging and tumor markers (tumor markers).

Research method

The type of research used in this research is library research or library research, namely research conducted through collecting data or scientific writings that aim at research objects or data collection that is a library in nature, or studies that are carried out to solve a problem that focuses on a critical and in-depth review of relevant library materials. A literature review builds concepts or theories that form the basis of studies in research. A literature review or literature study is an activity that is required in research, especially academic research, whose main objective is to develop theoretical as well as practical aspects. So by using this research method, the writer can easily solve the problem to be studied. Before conducting a literature review, the researcher must know what source the scientific information will be obtained from. Some of the sources used include; textbooks, scientific journals, statistical references, research results in the form of theses, theses, dissertations, the internet, and other relevant sources. After all the data has been collected, the next step is to analyze the data to draw a conclusion. The authors use content analysis techniques to obtain correct and precise results in analyzing data. Content analysis is research that is an in-depth discussion of the contents of written or printed information in the mass media.

Result and discussion

In this chapter, the author wants to show three research results that support the author's literature review. In the journal Breast Cancer Risk by Breast Density, Menopause, and Postmenopausal Hormone Therapy Use, Karla Kerlikowske *et al*. collected data from 587,369 women who used bilateral screening mammography as many as 1,349,027 examinations for their research. The study was linked to data from the Breast Imaging Reporting and Data System (BIRADS); data on female breast density was conducted by women aged 30 years or more by completing a questionnaire during an examination, and there is no history of having breast cancer or having had implants.

Not all the data of women who had mammography examinations were taken as research. The data used were only mammography examination data from 1 January 1996 to 31 December 2006. Not all women's data from the time mentioned were collected; some data lost Body Mass Index (BMI; 13.7%), without information about the use of hormone therapy (2.9%), and data without menopausal status (3.1%). The total data that was not collected due to incompleteness was 19.7%, and also, women who were examined after 31 December 2006 were not included in the data.

In that study, Karla Kerlikowske *et al*. related breast density, age, menopausal status, and use of hormone therapy by setting women at a BMI of 25 kg/m2.

Table 1: Five-year cancer risk estimates after a screening mammography examination by breast density, age, menopausal status, and HT use assuming BMI – 25 kg/m2

	BIRADS Breast Density*							
	1		2		3		4	
Age	5 Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI
Premenopausal‡								
30-34	0.3	0.0 to 0.9	0.5	0.2 to 0.7	0.9	0.6 to 1.3	0.7	0.2 to 1.1
35-39	0.1	0.0 to 0.3	0.7	0.6 to 0.9	1.1	0.9 to 1.2	1.5	1.2 to 1.7
40-44	0.4	0.2 to 0.5	0.9	0.8 to 0.9	1.5	1.4 to 1.6	1.8	1.7 to 2.0
45-49	0.7	0.5 to 0.9	1.3	1.2 to 1.4	2.1	1.9 to 2.2	2.5	2.3 to 2.7
50-54	0.8	0.4 to 1.1	1.5	1.4 to 1.7	2.3	2.1 to 2.5	**3.1**	**2.7 to 3.5**
Postmenopausal and no HT use‡								
30-45	0.2	0.1 to 0.5	0.7	0.5 to 1.0	1.1	0.7 to 1.4	1.2	0.5 to 1.9
45-49	0.5	0.2 to 0.7	0.8	0.7 to 1.0	1.6	1.3 to 1.8	2.2	1.6 to 2.7
50-54	0.6	0.5 to 0.8	1.3	1.2 to 1.4	1.8	1.6 to 1.9	2.2	1.8 to 2.6
55-59	0.8	0.6 to 0.9	1.7	1.6 to 1.8	2.4	2.3 to 2.6	2.4	2.0 to 2.8
60-64	1.1	1.0 to 1.3	2.0	1.9 to 2.1	2.7	2.5 to 2.9	2.8	2.2 to 3.4
65-69	1.2	1.1 to 1.4	2.3	2.2 to 2.5	**3.2**	**3.0 to 3.4**	**3.4**	**2.7 to 4.2**
70-79	1.7	1.5 to 1.9	2.6	2.5 to 2.7	**3.4**	**3.0 to 3.6**	**3.4**	**2.8 to 4.1**
80+	1.5	1.2 to 1.7	2.6	2.4 to 2.8	2.6	2.3 to 2.9	**3.5**	**2.4 to 4.5**
Postmenopausal and HT use‡								
30-45	0.3	0.1 to 0.5	0.6	0.4 to 0.7	1.1	0.8 to 1.3	1.1	0.7 to 1.6
45-49	0.5	0.3 to 0.8	0.9	0.8 to 1.1	1.5	1.3 to 1.7	2.2	1.8 to 2.7
50-54	0.6	0.4 to 0.8	1.3	1.2 to 1.4	2.3	2.1 to 2.4	2.8	2.5 to 3.2
55-59	0.8	0.6 to 1.0	1.8	1.7 to 2.0	**3.1**	**2.9 to 3.3**	**4.3**	**3.8 to 4.8**
60-64	1.0	0.7 to 1.2	2.0	1.9 to 2.2	**3.4**	**3.2 to 3.7**	**4.1**	**3.5 to 4.8**
65-69	1.6	1.2 to 2.0	2.3	2.1 to 2.5	**3.6**	**3.3 to 3.9**	**3.6**	**2.8 to 4.4**
70-79	1.5	1.2 to 1.9	2.9	2.6 to 3.1	**3.3**	**3.1 to 3.6**	**4.2**	**3.5 to 5.0**
80+	1.3	0.5 to 2.2	2.5	2.0 to 3.0	**4.3**	**3.6 to 5.0**	**4.4**	**2.5 to 6.2**

Abbreviations: HT, hormone therapy; BMI, body mass index; BIRADS, Breast Imaging Reporting and Data System.
*BIRADS density 1 = almost entirely fat (low breast density); 2 = scattered fibroglandular densities (average breast density); 3 = heterogeneously dense (high breast density); 4 = extremely dense (very high breast density).
†Risk estimates come from the partly conditional Cox proportional hazards models assuming interactions between HT use, menopausal status, and breast density using robust sandwich variance estimates to account for multiple mammography estimations per woman adjusting for age category, BMI, BMI2, interactions between BMI and BMI2 with menopausal status (since they were significant $P = .002$ and $P = .017$, respectively), E, E + P, and registry. Interaction terms use a hierarchical algorithm in which all lower order main effects or interactions are included in the model regardless of statistical significance. Risk estimates were calculated for women with a BMI = 25 kg/m^2 (approximate average BMI in population) and average registry (proportions of mammography examinations from each registry).
‡Premenopausal group with n = 3,856 breast cancers; postmenopausal no HT group with n = 5,700 breast cancers; postmenopausal HT group with n = 4,534 breast cancers.

From the table, it can be seen that the risk of postmenopausal hormone therapy users from ages 55 to 59 years or older to get breast cancer within five years is 3% higher, whereas postmenopausal women without using hormone therapy will have a risk of breast cancer after age 65 and over. The table shows that the use of postmenopausal hormone therapy in women with BIRADS-1 or BIRADS-2 type breast density has little effect on causing breast cancer. They also studied the 5-year risk of developing breast cancer in women aged 55 to 59 years with BIRADS-4 breast density on postmenopausal hormone therapy using estrogen-only (3.0%) and those using a mixture of estrogen and progestin (4.2%).

Table 2: Association between breast density and breast cancer risk by type of HT use among postmenopausal women with known hysterectomy status and 5-year breast cancer risk after a screening mammography examination across age groups for women with a BMI of 25 kg/m2

	BIRADS Breast Density*							
	1		2		3		4	
Variable	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI	5-Year Risk %†	95% CI
Postmenopausal E use‡								
30-45	0.4	0.3 to 0.5	0.7	0.6 to 0.7	1.1	1.0 to 1.2	1.3	1.1 to 1.6
45-49	0.6	0.4 to 0.7	0.9	0.8 to 1.0	1.4	1.3 to 1.6	1.8	1.5 to 2.1
50-54	0.7	0.6 to 0.9	1.2	1.1 to 1.3	1.8	1.7 to 2.0	2.3	1.9 to 2.6
55-59	0.9	0.7 to 1.1	1.5	1.4 to 1.7	2.4	2.3 to 2.6	3.0	2.6 to 3.5
60-64	1.1	0.9 to 1.4	1.9	1.7 to 2.0	2.9	2.7 to 3.2	3.6	3.1 to 4.2
65-69	1.3	1.0 to 1.6	2.1	2.0 to 2.3	3.4	3.1 to 3.6	4.2	3.5 to 4.8
70-79	1.4	1.1 to 1.7	2.3	2.1 to 2.5	3.6	3.4 to 3.9	4.5	3.8 to 5.2
80+	1.3	1.0 to 1.6	2.1	1.9 to 2.3	3.3	3.0 to 3.7	4.1	3.4 to 4.8
Postmenopausal E + P‡								
30-45	0.4	0.3 to 0.5	0.9	0.8 to 1.0	1.4	1.3 to 1.5	1.9	1.6 to 2.1
45-49	0.5	0.4 to 0.7	1.2	1.1 to 1.3	1.9	1.7 to 2.0	2.5	2.2 to 2.8
50-54	0.7	0.5 to 0.9	1.5	1.4 to 1.6	2.4	2.2 to 2.6	3.2	2.8 to 3.5
55-59	0.9	0.7 to 1.1	2.0	1.9 to 2.2	3.2	3.0 to 3.4	4.2	3.7 to 4.6
60-64	1.1	0.8 to 1.4	2.4	2.3 to 2.6	3.8	3.6 to 4.1	5.0	4.5 to 5.6
65-69	1.3	1.0 to 1.6	2.8	2.6 to 3.0	4.4	4.1 to 4.7	5.8	5.1 to 6.4
70-79	1.4	1.0 to 1.7	3.0	2.8 to 3.2	4.7	4.4 to 5.0	6.2	5.5 to 6.9
80+	1.2	0.9 to 1.6	2.8	2.5 to 3.0	4.3	3.9 to 4.7	5.7	5.0 to 6.4

They found that among women with high breast density, postmenopausal hormone therapy with estrogen and progestin therapy was associated with an increased risk of breast cancer than those not using hormone therapy. Research states that estrogen without progestin hormone therapy does not have a big or small effect on causing breast cancer.

The probable mechanism for women with high breast

density and the influence of hormone therapy in increasing the risk of breast cancer is not known. The use of hormone therapy in postmenopausal women can inhibit the process of breast involution during aging, resulting in an increased risk of breast cancer. Alternatively, the condition of women with high breast density combines with the presence of endogenous estrogen and progesterone when women are in the premenopausal process, and the presence of exogenous estrogen and progesterone therapy when women are in the postmenopausal process can stimulate the proliferation of epithelial cells and stromal cells in the breast. Breast is associated with high breast density, increasing the risk of tumors and breast cancer.

The Evolution of breast cancer incidence concerning hormone replacement therapy use in Belgium, which was studied by C. Antoine *et al*., stated that after the publication of results regarding the relationship of hormone replacement therapy or HRT from WHI (Women's Health Initiative), the demand for and sales of therapy decreased dramatically. [25] in several countries. Several studies state the association of these changes with a reduced incidence of breast cancer.

Analytical data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Registries show a reduction in the incidence of breast cancer between 2002 and 2003, followed by a statement from the WHI and a decrease in the use of hormone replacement therapy by postmenopausal women in the United States [26]. In Germany, the incidence of breast cancer decreased from 2001 to 2005 for those aged 50 and over. Belgium is one of the European countries with high use of hormone replacement therapy. In their study, they compared three regions in Belgium (Flanders, Wallonia, and Brussels) on the relationship between the incidence of breast cancer and sales of hormone replacement therapy.

Standard accounting data for breast cancer (per 100 000 women) aged 50-69 years in Belgium (Brussels, Flanders, Wallonia) is provided by the Belgian Cancer Registry (www.registreducancer.org). There is no incidence data for ages 40-49 years. Data taken from Flanders is for 1999-2006, and for Brussels and Wallonia is for 2004-2006. IMS Health provided hormone replacement therapy sales data (www.imshealth.com) in 1997-2008 for Brussels, Flanders, and Wallonia.

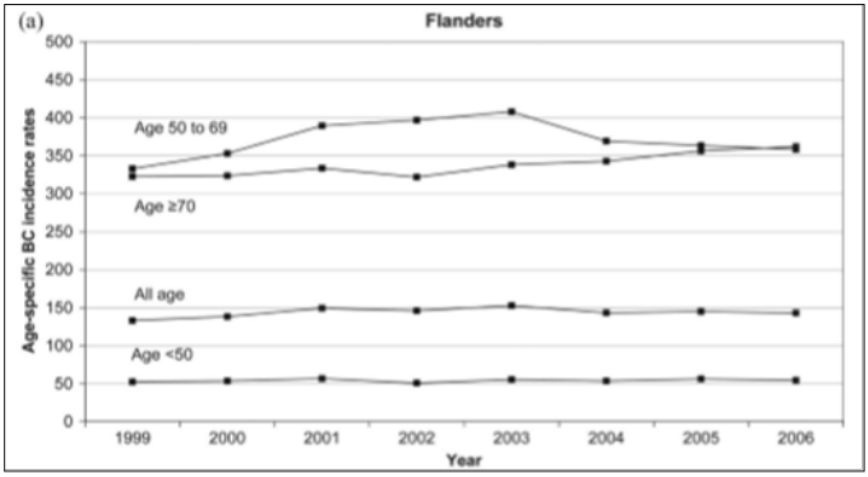

Fig 1: Age-specific Breast Cancer (BA) in Flanders

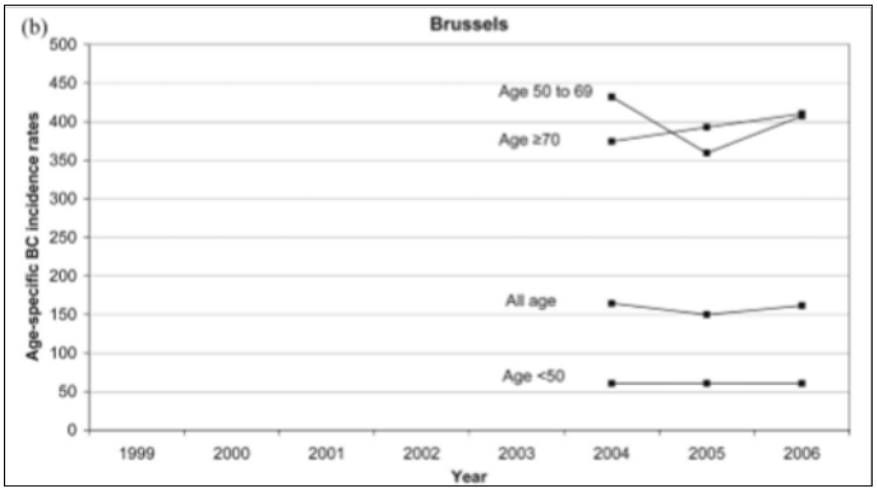

Fig 2: Age-specific Breast Cancer (BA) in Brussels

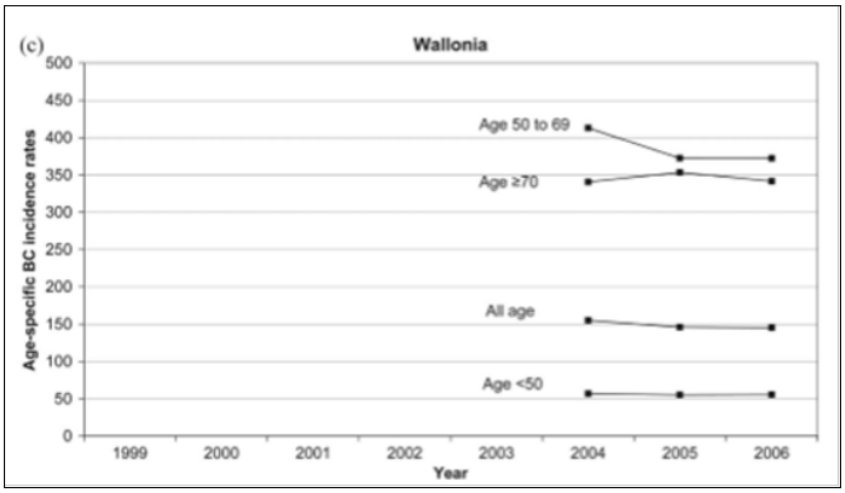

Fig 3: Age-specific Breast Cancer (BA) in Wallonia, Belgium

Belgium is one of the countries with the highest incidence of breast cancer in Europe. The highest incidence of breast cancer is in Brussels, Wallonia, and finally in Flanders. Breast cancer incidence decreased from 2003 onwards in Flanders, Brussels, and Wallonia, especially in the 50-69 age group. In the same three regions, HRT uses halved from 2002 onwards. Greater reductions were observed for estrogens combined with androgenic progestins, estrogens alone, and estrogens prescribed with separate progestins. The correlation between breast cancer incidence and HRT sales in the previous year was 0.55 (p¼0.04); however, adjusting for the number of women in the 40-69 year age class in each region, the correlation was no longer statistically significant (r¼0.39, p¼0.17).

Likewise, the journal Breast Cancer Incidence and Hormone Replacement Therapy in Canada by Pritwish De *et al*. The journal stated that in 2002 after a statement from WHI about its clinical trials indicating the long-term risk of breast cancer from the use of combined estrogen and progestin hormone replacement therapy, the more important health benefits for postmenopausal women. A decrease followed the decrease in the use of hormone replacement therapy in the incidence of breast cancer in several countries. The study aims to prove whether there is a decrease in the use of hormone replacement therapy in Canada.

Data on prescriptions for hormone therapy were obtained from the national pharmacy prescription registry filled in to confirm reported trends in the use of hormone replacement therapy among approximately 1,200 women aged 50-69 years who participated in the National Population Health Survey between 1996 and 2006 and whose data were extrapolated to the population. Canadian girl. Age-standardized incidence rates for breast cancer were obtained from the population-based Canadian Cancer Registry for the same period, and mammography rates were obtained from the Public Health Survey of Canada. Joinpoint regression examined changing hormone replacement therapy use trends and breast cancer incidence.

The reduced frequency of use of hormone replacement therapy was reflected in the decline in prescriptions of hormone therapy dispensed after 2002. The largest decrease was in the use of combined hormone replacement therapy (from 1.7%, 95% confidence interval [CI] = 10.1% to 14.2%, 4.9%, 95% CI = 3.4% to 6.8%, of all women) occurred between January 1, 2002, and December 31, 2004, among women aged 50-69 years. This decrease coincided with a 9.6% reduction in the incidence rate of breast cancer (from 296.3 per 100 000 women, 95% CI = 290.8-300.5 per 100 000 women, at 2002-268.0 per 100 000 women, 95% CI = 263.3 to 273.5 per 100 000 women, in 2004). Over 2002-2004, there was an association between decreased use of hormone replacement therapy and breast cancer incidence among Canadian women aged 50-69, with no change in mammography rates.

Conclusion

Hormone replacement therapy is a therapy to reduce menopausal symptoms. This therapy will be used during post-menopause. The therapy that many thought could help reduce menopausal symptoms had a negative impact. The use of these therapies, which are also influenced by age, menopausal status, breast density, etc., can affect the increase in the incidence of breast cancer. Hormone replacement therapy is divided into 2, namely therapy with the hormone estrogen and hormone replacement therapy with the hormones estrogen and progestin. The reason for the increased incidence of breast cancer is still idiopathic, or the cause is unknown. However, in K. Karlowske's research, it was stated that the possibility of hormone replacement therapy or the addition of hormones to a person could increase breast density and affect cell proliferation which causes cancer cells.

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