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Hormonal contraception increases risk of breast tumor based on clinical breast examination among adult women

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ABSTRACT

BACKGROUND
In Indonesia, cancer prevalence according to the Basic Health Research 2013 was 1.4 per 1000 inhabitants and the most common cancer in hospitalized patients in 2010 was breast cancer (28.7%). Hormonal contraception (HC) use increases the breast cancer risk, even though HC has been used by 210 million women in the world. We aimed to define the association of HC with breast tumors based on clinical breast examination (CBE).

METHODS
A case-control design using secondary data from the baseline of the Cohort Study on the Risk Factors of Non-Communicable Disease (RFNCD) in 2011-2012 in 5 villages in Central Bogor District, Bogor City. Samples consisted of 152 cases and 152 controls. Cases comprised palpable tumors in one or both breasts CBE (+). Controls had no tumors in both breasts / CBE(-). Data were analyzed by logistic regression.

RESULTS
Odds Ratio (OR) of CBE + was 1.83 (95% CI: 1.11-3.04; p=0.019) for HC user and 1.62 (95% CI: 1.01-2.60; p=0.044) for blood total cholesterol level <200 mg/dL. OR of group CBE(+) was 1.01 (current smokers) and 0.49 (former smokers) compared with nonsmokers (p=0.082); OR was also 1.21 for subjects with one child and 1.77 for those without children, compared with those who had ≥2 children (p=0.454).

CONCLUSION
Hormonal contraception use increases breast tumor risk 1.8-fold after controlling for total cholesterol, smoking status and parity. With the several limitations of this advanced analysis, investigations focused on types and duration of HC use are still necessary.

Keywords: Hormonal contraception, breast tumor, adult women

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INTRODUCTION

Cancer is the principal cause of death in advanced countries and the second main cause of death in developing countries.[1] Breast cancer is the most common cause of death from cancer in women (with 522,000 deaths in 2012) and is also the type of cancer occurring most frequently in women in 140 out of 184 countries.[2] The prevalence of cancer in Indonesia based on interview results in the Basic Health Research (Riskesdas) for 2013 was 1.4 per 1000 population and cancer was the seventh leading cause of death (5.7%) from all-cause mortality. The most frequent type of cancer in hospitalized patients throughout Indonesia in 2010 was breast cancer (28.7%).[3]

The risk factors for breast cancer are among other things age, family history of breast cancer and reproductive factors characterized by exposure to sexual hormones (i.e. estrogen and progesterone in women).[4] Both hormones are contained in hormonal contraceptives (HC). Oral contraceptives contain estrogen and progesterone, whereas the mini pills, contraceptive injections, and implants contain progesterone.[5,6] The results of epidemiological and clinical research showed strong evidence on the role of estrogen/ progesterone in the formation of breast cancer, but the exact mechanism of tumor formation is not yet completely understood. [7,8] According to Urban et al., [9] there was an increased risk of breast cancer associated with the use of HC, i.e. pills and/or injections (OR=1.66; 95% CI: 1.28 - 2.16; p<0.001), pills only (OR=1.57; 95% CI: 1.03-2.40; p=0.04), injections only (OR=1.83; 95% CI: 1.31-2.55; p<0.001). The results of an analysis by Sihombing and Sapardin [10] from data of the Cohort Study on Risk Factors of Non-communicable Disease (RFNCD) *[Studi Kohor Faktor Risiko Penyakit Tidak Menular* (FRPTM)*]* showed that the use of contraceptive pills has a risk of 3.63-fold for causing tumors of the breast based on ultrasonography [USG] (95% CI: 1.63-8.10; p=0.002). This finding differs from that of an analysis by Sirait et al.[11] from Riskesdas 2007 data, who did not find a significant relationship between the use of contraceptive pills and tumor/cancer breast based on interviews (aOR=0.74; 95% CI: 0.50-1.08; p=0.117). In Indonesia, the percentages of HC users were: for injections 38.5%, pills 31%, and implants 12.3%.[10]

The novelty of this study lies in the diagnosis of breast tumors by means of clinical breast examination (CBE), because in the RFNCD cohort study the CBE results were a determinant for performing or not performing USG.

The reason for selecting CBE as a method of early detection is because the study by Zafar [12] showed that standardized CBE can differentiate between benign and malignant tumors. Structured CBE in patients with breast tumors has a sensitivity of 100% (95% CI: 0.8-1) and a specificity of 94.6% (95% CI: 0.86-0.97) and the likelihood ratio for breast carcinoma is 17.8 (95 % CI: 7.6-41.7). The study by Ravi and Rodriguez [13] found that among 15 cases of malignancy in patients who underwent mammography followed by histopathological confirmation, CBE detected one case of malignancy that had been overlooked in the mammogram. The research carried out by Khoda and Kapa [14] in 50 female patients with clinically palpable breast lump(s) found on CBE, the lumps in 40 (80%) patients had benign and 8 (16%) had malignant features. However, 2 (4%) patients were found to be in the "suspicious" category. On histopathological examination, 36 benign tumors were confirmed as such, but 4 were found to be malignant. All of 8 malignant tumors found by CBE were confirmed by histopathological examination. In the analysis of data from the previous RFNCD cohort study on tumors/cancers of the breast,[10] there was no definition of the contraceptive pill variable, because in the questionnaire there was no specific question to differ between respondents who used one type of HC and those who used more than one type of HC (combined HC). Because of this limitation, HC as the main independent variable in the present paper was defined as contraception using pills or

injections or implants. Results of several investigations showed that a higher total cholesterol concentration (TCC) has a decrease risk for tumors/cancers of the breast than a lower TCC. To determine the odds ratio of lower TCC (<200 mg/dL) against breast tumors, in this analysis high TCC (≥200 mg/dL) as another independent variable was positioned as a reference.

In Indonesia, data about breast tumors/ cancers are generally data from patients attending hospitals, who are usually already in an advanced stage. In 2016 the Indonesia Agency for Research and Development, Ministry of Health *(Badan Penelitian dan Pengembangan Kesehatan)* conducted a national research of non-communicable disease that focused on breast tumors in the community, but the report is still in the process of finalization. According to Poosari et al.[15], epidemiological research and risk factors for breast cancer are very important in its prevention. The use of HC is a risk factor for breast cancer, but the magnitude of the risk is not yet clear. Therefore, the aim of this further analysis was to determine the magnitude of the risk of HC use for the development of breast tumors based on CBE.

METHODS

Design of the study

A case-control study was conducted using secondary data from the baseline of the RFNCD cohort study that had been performed in the years 2011-2012.

Subjects

The respondents were permanent residents aged 25-65 years in 5 *kelurahan* (villages) of Central Bogor District – Bogor City, i.e. Kebon Kalapa, Babakan Pasar, Babakan, Ciwaringin and Panaragan.The inclusion criterion was: female respondents who had already undergone CBE during the execution of the RFNCD cohort study and whose data were complete. The exclusion criterion was respondents who were pregnant or had been breastfeeding for equal or less than 6 months.

The 152 cases with positive CBE results (CBE(+)) i.e. the presence of a tumor in one breast or both breasts, which were found in the RFNCD cohort study, were all included in the study sample. This number has met the minimum sample requirements which calculated with the formula of hypothesis testing for the odds ratio for case control studies, with a level of significance of 95% (α=5%) and power of 95% (β=5%). The OR that was considered to be significant was 3.6 and the estimated proportion effect in the controls was 0.657, which was taken from the study results of Sihombing and Sapardin.[10] The controls were respondents with negative CBE results i.e. no presence of a tumor in both breasts. The selection of the controls was performed in a ratio of 1:1 by simple random sampling, and they were not paired (unmatching), so that the analyzed data totalled 304 respondents, consisting of 152 cases and 152 controls.[16]

Questionnaire

The sociodemographic data that were collected as a result of the questionnaire-based interviews consisted of: 1) age (<40 years and ≥40 years);[10] 2) education i.e. low (no formal education, not having finished elementary school, and finished elementary school), middle (junior high school and senior high school) and high (D3/ D4 and university);[17] 3) marital status i.e. have a partner (married) and have no partner (single or divorced/widowed).[15] This grouping was used because there were very few respondents with single status, comprising only 10 subjects (3.3%). Data about risk factors consisted of: 1) smoking status, i.e. nonsmoking (never smoked), former smoking (occasionally or daily) and current smoking (occasionally or daily);[18] 2) mental/emotional disorder was measured using the Self-Reporting Questionnaire instrument with 20 items of question (SRQ-20). The respondents were considered having a mental/emotional disorder if they answered "yes" to minimally 6 out of 20 questions in the instrument;[19] 3) parity/

number of deliveries was calculated from the total number of children that were born (own children), divided into 3 groups, i.e. "no children", "1 child" and "2 children or more";[20] 4) breastfeeding experience i.e. "breastfeeding for <6 months or never did breastfeeding", and "breastfeeding for ≥6 months";[21] 5) HC users (respondents who ever had sexual intercourse) were respondents who had ever used or were currently using contraceptive pills, injections or implants. The responses were divided into 2 categories, i.e. "yes" and "no".[15] The use of hormone-replacement therapy (HRT) and consumption of hormonal medications (treatment for infertility) was not incorporated in this analysis since the data were very few in number. Regarding the foods/beverages that were habitually consumed, the respondents were asked according to the Food Frequency Questionnaire (FFQ); for example, consumption of milk, coconut milk, fried snacks and packaged beverages. Each type was divided into two categories, i.e. "≥3 times per week (frequent)" and "<3 times per week (seldom)".[22]

Measurements

Anthropometric measurement was performed according to the Guide to Examination and Measurement of the RFNCD cohort study (unpublished). The respondents were advised to use loose and thin clothing. Body weight (BW) was measured using AND type UC-322 digital scales with a capacity of 150 kg and precision of 50 g. The respondents were asked to stand without footwear. Height was measured in the upright position using a "multifunction" measuring tool. The body mass index (BMI) was obtained by the following formula:

$$BMI = BW\ (kg) / height\ (m)^2$$

Based on the classification of the South Asian Health Foundation, the BMI is divided into 4 categories, i.e. underweight (BMI <18,5), normal (18.5-22.9), overweight (23-24.9), obesity (≥25).[23,24] In the present analysis the BMI was only assigned into 2 categories, i.e. ≥25 and <25.[10]

Clinical breast examination

In the CBE procedure, visual inspection and palpation was performed according to the Guide to Examination and Measurement of the RFNCD cohort study (unpublished). The CBE positive respondents were those who had a palpable tumor in one breast or both breasts (right/left). The CBE was performed by the midwife of the primary health care *(puskesmas)* who had been trained by a specialist in oncologic surgery from Dharmais Hospital – Jakarta.

Laboratory blood analysis

For the determination of blood lipid concentration, the respondents were asked to fast for 12-14 hours, from the night before the examination until the next morning. The respondents were only permitted to drink water. With the respondents in the fasting condition, venous blood samples were drawn from them. The lipid profile comprised TCC (<200 mg/dL and ≥200 mg/dL); triglycerides (<150 mg/dL and ≥150 mg/dL); low density lipoprotein cholesterol (LDL) (<100 mg/dL and ≥100 mg/dL); high density lipoprotein cholesterol (HDL) (≥50 mg/dL and <50 mg/dL).[25] Blood chemistry investigation was performed by Prodia Laboratory in Bogor City.

Data analysis

Bivariate analysis (chi-square test) was performed to determine the presence or absence of a difference in proportions between the dependent and independent variables, followed by multiple logistics regression analysis to determine the level of HC user risk for the presence of breast tumors based on CBE, by controlling for other variables.[26]

Ethical clearance

The RFNCD cohort study had already received ethical clearance from the Commission on Health Research Ethics of the Indonesia Agency for Research and Development, Ministry of Health *(Badan Penelitian dan Pengembangan Kesehatan)* under No. KE.01.08/EC/485/2011

dated 10 August 2011 and No. KE.01.05/EC/394/ 2012 dated 11 May 2012.

RESULTS

Among the 2955 female respondents who underwent CBE in the RFNCD cohort study were found 152 CBE(+) cases (5.14%). The marital status of the majority of the respondents was "married/divorced/widowed" and only 10 (3.3%) of the 304 persons were single. Among 231 contraceptive users, 184 persons (79.7%) were current users or had ever used hormonal family planning, comprising 165 persons (89.7%) with married marital status and 19 persons (10.3%) with divorced marital status. Table 1 shows that more than half of the respondents, in both the CBE(+) and CBE(-) groups, were more than 40 years old, half of the CBE(+) group being of low educational level, with BMI of <25 and total cholesterol concentration (TCC) of <200 mg/dL. A large proportion of the CBE(+) group comprised respondents with triglyceride concentration of <150 mg/dL, LDL ≥100 mg/dL, and HDL ≥50 mg/dL, who were not yet in menopause. While in the CBE(-) group, more than

Table 1. Characteristics of respondents based on positive and negative CBE

Characteristic	CBE				p value
	Positive		Negative		
	n	%	n	%	
Age (years)					0.340
<40	59	38.8	51	33.6	
≥40	93	61.2	101	66.4	
Education					0.492
High	11	7.2	11	7.2	
Middle	78	51.3	68	44.7	
Low	63	41.4	73	48.0	
Marital status					0.882
Married	124	81.6	125	82.2	
Single/divorced	28	18.4	27	17.8	
BMI (kg/m^2)					0.038
<25	79	52.0	61	40.1	
≥25	73	48.0	91	59.9	
Total cholesterol (mg/dL)					0.021
≥200	71	46.7	91	59.9	
? 200	81	53.3	61	40.1	
Triglycerides (mg/dL)					0.156
≥150	14	9.2	22	14.5	
<150	138	90.8	130	85.5	
LDL (mg/dL)					0.216
≥100	123	80.9	131	86.2	
<100	29	19.1	21	13.8	
HDL (mg/dL)					0.720
<50	53	34.9	56	36.8	
≥50	99	65.1	96	63.2	
Menopause					0.180
Yes	45	29.6	56	36.8	
No	107	70.4	96	63.2	

*Tumor diagnosis based on CBE : clinical breast examination

half were respondents with low educational level, with BMI ≥25 and TCC ≥200 mg/dL. A large proportion in the CBE(-) group were respondents with triglyceride concentration of <150 mg/dL, LDL ≥100 mg/dL, HDL ≥50 mg/dL and who were not yet in menopause.

Table 2 shows that both in CBE(+) and CBE(-) groups, a larger proportion were nonsmoking, had no stress, had ≥2 children, with a duration of breastfeeding of ≥6 months, without family history of breast cancer, with consumption of fried foods, milk, coconut milk and packaged beverages of <3 times per week. In the CBE(+) group, it was apparent that the percentage of HC users was double that of the non-users, while in the CBE(-) group, there were almost no differences between HC users and non-users.

From the results of multivariate analysis (Table 3), the odds ratio of HC users was 1.8-fold greater (aOR=1.83; 95% CI: 1.11-3.04) than those of non-users, after controlling for TCC, smoking status, and parity. The odds ratio in the CBE(+) group in respondents with TCC <200 mg/dL was 1.6-fold greater (aOR=1.62; 95% CI: 1.01-2.60) those that of the respondents with TCC ≥200 mg/dL. The OR of current smoking was 1.01 (95% CI: 0.52-1.96) and those of former smoking 0.49 (aOR=0.49; 95% CI: 0.26-1.93), as

Table 2. Risk factors for breast tumors based on positive and negative CBE

Risk factor	CBE				p value
	Positive		Negative		
	n	%	n	%	
Smoking status					0.188
Nonsmoking	109	71.7	99	65.1	
Former smoking	20	13.2	32	21.1	
Current smoking	23	15.1	21	13.8	
Stress					0.803
No	107	70.4	105	69.1	
Yes	45	29.6	47	30.9	
Parity (no. of children)					0.728
≥2 children	111	73.0	117	77.0	
1 child	29	19.1	25	16.4	
without or as yet without a child	12	7.9	10	6.6	
Duration of breastfeeding					0.428
≥6 months	126	82.9	131	86.2	
< 6 months/never	26	17.1	21	13.8	
Hormonal contraception					0.035
No	51	33.6	69	45.4	
Yes	101	66.4	83	54.6	
Family history of breast cancer					1.000
Absent	146	96.1	146	96.1	
Present	6	3.9	6	3.9	
Consumption of fried foods					0.398
<3 times/week	103	67.8	96	63.2	
≥3 times/week	49	32.2	56	36.8	
Milk consumption					0.435
<3 times/week	109	71.7	115	75.7	
≥3 times/week	43	28.3	37	24.3	
Coconut milk intake					0.523
<3 times/week	112	73.7	107	70.4	
≥3 times/week	40	26.3	45	29.6	
Consumption of packaged beverages					0.368
<3 times/week	122	80.3	128	84.2	
≥3 times/week	30	19.7	24	15.8	

* Tumor diagnosis based on CBE: Clinical breast examination

Table 3. Multiple logistic regression analysis of risk factors for braest tumors in adult women

Risk factor	Crude OR	95% CI	p	Adj OR	95% CI	p value
Hormonal contraception						
No	1.00	Reference		1.00	Reference	
Yes	1.65	1.04 – 2.62	0.035	1.83	1.11 – 3.04	0.019
Total cholesterol						
≥200 mg/dL	1.00	Reference		1.00	Reference	
<200 mg/dL	1.70	1.08 –2.68	0.022	1.62	1.01 – 2.60	0.044
Smoking status						
Non-smoking	1.00	Reference		1.00	Reference	
Former smoking	0.57	0.31 – 1.06	0.074	0.49	0.26 – 1.93	0.028
Current smoking	0.99	0.52 – 1.91	0.987	1.01	0.52 – 1.96	0.987
Parity (no. of children)						
≥2 children	1.00	Reference		1.00	Reference	
1 child	1.22	0.68 – 2.22	0.507	1.21	0.65 – 2.25	0.555
None	1.27	0.53 – 3.05	0.600	1.77	0.69 – 4.53	0.234

* Adjusted odds ratio controlled for variables in this table; ** Tumor diagnosis based on CBE

compared with respondents who were nonsmoking, but this difference was statistically not significant. Similarly with parity, although the adjusted odds ratio (aOR) of CBE(+) respondents was 1.21 (95% CI: 0.65-2.25) for those who have only one child and 1.77 (95% CI: 0.69-4.53), for those who have no children, was higher than in the respondents with ≥2 children, this result was also not statistically significant. In this connection, smoking status and parity are confounding variables, that if excluded from the multivariate analysis causes changes in OR of HC (as the principal independent variable) >10%.

DISCUSSION

The respondents who used HC had a 1.8-fold greater risk for developing breast tumors as compared with those who were non-users. This is according to the study results of Urban et al.[9] who showed an increase in the OR of breast cancer in users of contraceptive pills and/or injections. Poosari et al.[15] found an increased risk of breast cancer of 1.31 times in HC users, which was however statistically non-significant (95% CI: 0.65-2.65).

In general, with regard to HC composition, the pills contain estrogen and progesterone, whereas the mini pills, injections and implants contain progesterone.[5,6] Artoum et al.[27] state that estrogen contribute to the development of tumors by promoting cell proliferation and mutation or by increasing the probability of mutations that regulate growth and differentiation of mammary cells that may play an important role in the growth of breast cancers. According to Sirait et al.,[11] the growth of mammary tissues is very sensitive to estrogen, therefore females with long-term exposure to estrogen will carry a high risk for the occurrence of breast cancer. Breast cancer is characterized by the loss of estrogen receptors (ERs) that is associated with aggressive pathology and a low level of estimated recovery (prognosis).[28]

Before the publication of the study results of Women's Health Initiative (WHI) in the US in 2002, many experts were of the opinion that the increased risk of breast cancer observed in HRT research was due to the effect of estrogen. After the WHI results had found, the focus changed to progesterone, which was considered to increase cell division and accumulation of damaged DNA. The highest proliferative activity occurs in the luteal phase of the menstrual cycle (when the endogenous progesterone concentration is high).[29] Daniel et al.[8] state that progestin added to HRT significantly increases the incidence of breast tumors and the breast tumor stage in females who are in menopause. Therefore progesterone is no longer considered a completely

safe alternative. According to Lanari,[30] more than 70% of breast cancers express the estrogen receptor alpha (ERα) and respond to antiestrogen therapy. These cancers also express progesterone receptors that are reliable markers for estrogen receptors.

The results of research by Llanos et al.,[31] Shah et al.,[32] Melvin et al.[33] and Ni et al.[34] showed that higher TCC has a less risk for breast tumors/cancers than lower TCC, therefore in the present further analysis TCC of ≥200 mg/dL (high) is positioned as reference for determining the odds ratio of TCC of <200 mg/dL (low). The multivariate results show that TCC <200 mg/dL actually increases the risk of breast tumors by 1.6-fold as compared with TCC of ≥200 mg/dL. This is in line with the study results of Llanos et al.[31] who state that there is an inverse relation between the risk of breast cancer and TCC (OR=0.46; 95% CI: 0.25-0.85), in other words, TCC in the cases was significantly lower (189.3 mg/dL) as compared with the controls (206.8 mg/dL). Similarly, the study results of Shah et al.[32] found that higher TCC was significantly associated with a decreased risk of breast cancer (OR=0.30; 95% CI: 0.12-0.76). While Melvin et al.[33] and Ni et al.[34] found that higher TCC has a lower risk for breast cancer, although results were not statistically significant, i.e. HR=0.97 (95% CI: 0.89-1.05) and RR=0.96 (95% CI: 0.86-1.07), respectively. These results differed with those of a study by Kitahara et al.[35] who state that higher TCC (≥240 mg/dL) is positively associated with breast cancer (HR=1.17; 95% CI: 1.03-1.33). There are also the results of the study by Hu et al.[36] who found that higher TCC increases the risk of breast cancer (OR=1.45; 95% CI: 1.14-1.85). Likewise, the study by Peela et al.[37] found significantly increased TCC in patients with breast cancer. Llaverias et al.[38] state that in general the role of cholesterol in the initiation and development of tumors is very controversial. Low cholesterol concentrations are known to be used as a cancer marker, and several types of cancer appear to decrease plasma cholesterol level. This is the result of increased utilization of cholesterol by the tumors for their development. Thus the increased plasma cholesterol level accelerates the development and increases the aggressivity of the tumors. From the results of the study by McDonell et al.[39] it is known that cholesterol does not play a direct role in tumor pathogenesis, but cholesterol or its derivatives function as marker molecule in cancer cells. Cholesterol is the raw material for the biosynthesis of steroid hormones, one of them being estradiol (estrogen).[40,41] According to Llaverias et al.[38] an important aspect that has to be considered when testing the correlation between plasma cholesterol and breast cancer is that the estrogen concentration is also associated with plasma HDL cholesterol.

In the present analysis it was found that the relationship between smoking status and the risk of breast tumors was statistically not significant (aOR=0.49) for former smoking and aOR=1.01 for current smoking, as compared with nonsmoking. Comparatively identical results were found by Xue et al.[18] in their research the HR=1.06 (95% CI: 1.01-1.11) for former smoking and HR=1.09 (95% CI: 1.02-1.17) for current smoking, after controlling for age at menopause, menopause status and use of hormones post-menopause as compared with nonsmoking. Pasarelli et al.[42] even differentiate the risk of smoking between 1 year before and 1 year after diagnosis of breast cancer. Individuals who for 1 year before diagnosis of breast cancer were active smoking, had a 1.3-fold higher risk of dying from breast cancer (HR=1.25; 95% CI: 1.13-1.37) as compared with nonsmoking. While 10% of females who continued to smoke after diagnosis, had a 1.7-fold higher risk of dying from breast cancer (HR=1.72; 95% CI: 1.13-2.60), as compared with nonsmoking. According to Bjerkaas et al.,[43] several large prospective cohort studies have found that smoking can cause breast cancer, especially in females who smoke for an extended period of time, those who smoke a great number of cigarettes per day and those who smoke before delivering their first child. Their research results showed that the mortality from breast cancer may indeed be low, but increases

significantly for active smoking (current) and former smoking (HR=1.15; 95% CI: 1.01-1.32 and HR=1.15; 95% CI: 1.02-1.30, respectively), as compared with nonsmoking. Based on the study by Bishop et al.[44] it is known that the relative mortality risk from breast cancer is 1.44 for current smoking (95% CI: 1.01-2.06) and 1.13 for former smoking (95% CI: 0.66-1.94), as compared with nonsmoking.

In the present study it was found that respondents with 1 child had an aOR=1.21 and that respondents who have no children, had an aOR=1.77, which is greater than in respondents who have ≥2 children. However, these results were statistically not significant, Sirait et al.[11] found that persons who have no children have a 1.97-fold greater risk (95% CI: 1.24-3.14) and that those who have 1 child have a 1.64-fold greater risk (95% CI: 1.16-2.33) that is statiscally significant as compared with persons who have 4 children. With reference to the statement of Shen et al.,[45] in that increased parity (the number of deliveries) is a protective factor against breast cancer, because parity decreases estrogen/progesterone receptor-positive breast cancers and breastfeeding (lactation) decreases the risk of receptor positive or negative breast cancers or both. Heys et al.[46] state that estrogen increases during pregnancy then decreases post-delivery until around 1 year. Futhermore, breastfeeding temporarily decreases estrogen post-delivery. The concentration of estrogen during the ovulatory cycle is lower after the first pregnancy when compared with females who have never borne any children. This differs from the results of the study by Sun et al.[20] who showed that subjects who had 1-2 children had a 1.32-fold greater risk of suffering from breast cancer (95% CI: 0.89-1.95), while subjects who had ≥3 children had a 1.77-fold greater risk of suffering from breast cancer (95% CI: 1.18-2.66) as compared with subjects who had never borne any children.

Thus it can be explained that the exogenous steroid hormones (estrogen/progesterone) contained in HC promote tumor cell proliferation and accumulate DNA damage.[29] Low cholesterol concentrations are known to be able to become cancer markers. This is caused by the increased utilization of cholesterol by the tumors for their development. The increased concentrations of plasma cholesterol, which is the raw material for the biosynthesis of steroid hormones, accelerates the development and increases the aggressivity of tumors.[38] In addition, the substances contained in cigarettes, such as nitrosamine and nicotine, can also be carcinogenic. Nitrosamine induces cancers by causing gene and/or DNA mutations, while nicotine promotes cancer cell development.[47] Meanwhile, parity (the total number of children) is a measure of a life-long exposure to endogenous steroid hormones (from pregnancy and delivery up to the lactation period). Exposure to high concentrations of exogenous or endogenous steroid hormones is associated with the risk of breast cancer.[29]

The limitations of the present study are as follows. First, there are no data on the total number of cigarettes smoked per week by the occasional smoking; second, there is no separate question for respondents who use one type of HC and for those who use more than one type of HC (combined HC) and for duration of use; third, there is no question about whether or not HC was used continuously; and fourth for respondents who had ever used HC, there is no question about the duration of cessation of HC use, because according to the study results of Cibula et al.,[48] the effect of HC (pills) on the risk of breast cancer will disappear after cessation of the use of the contraceptive pills for 5-10 years. It is recommended that future studies, especially about questions on the type and duration of HC use may be more focused, so that the results will be increasingly improved.

CONCLUSION

Hormonal contraceptive (HC) users had a 1.8-fold increased risk of breast tumors after controlling for TCC (≥200 mg/dL=reference), smoking status and parity (≥2 children= reference).

CONFLICT OF INTEREST

The author declare that there is no conflict interest in this article.

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CONTRIBUTORS

ST contributed to the literature search, data analysis and writing of the draft. ANS contributed to "data cleaning" before data analysis (particularly that associated with CBE) and literature search. All authors read and approved the final manuscript.

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