Title:

Short breastfeeding duration is associated with premature onset of female breast cancer

Authors:

Ángel Fernández-Aparicio, RN[1], Jacqueline Schmidt-RioValle, PhD, RN[1], Pedro A. García, PhD[2], Emilio González-Jiménez, PhD, RN[1]

Affiliations:

1) Department of Nursing, Faculty of Health Sciences, University of Granada, Av. Ilustración, 60, 18016, Granada, Spain.

2) Department of Statistics and O.R, University of Granada, (Spain).

Corresponding author: Jacqueline Schmidt-RioValle, Department of Nursing, University of Granada, Avenida Ilustración, 60, (18016), Granada, Spain. Telephone: +34 958248291. E-mail: jschmidt@ugr.es

ABSTRACT

Currently, there is controversy concerning potential factors that contribute to the development of breast cancer. Our study analyzed the possible association between weight status, cigarette consumption, lactation period, serum estrogen levels, family history of breast cancer, and age at breast cancer diagnosis. We conducted a retrospective study at a University Hospital in Granada (Spain) by consulting the medical records of 524 women aged 19 to 91 years, all of them diagnosed and treated for breast cancer from 2011 to 2019. Our findings indicated that in non-morbidly obese females who were also non-smokers, a maternal lactation period of more than three months ($p = 0.013$) and the absence of family antecedents of cancer ($p = 0.025$) were statistically significant factors that led to a more advanced age at breast cancer diagnosis. Thus, maternal lactation seems to have a potential protective effect on breast cancer.

Keywords: Breast cancer, Obesity, Breastfeeding, Disease prevention.

Introduction

The most typical type of cancer in women is the breast cancer (Dudarev et al., 2013; Ferlay et al., 2015). According to Siegel et al. (2016), in 2016 in the United States of America (USA), there will be an estimated 249.260 new cases of cancer and 40.890 cancer deaths. In developed countries, breast cancer is the leading cause of cancer death in women 20 to 59 years of age. It is also worth mentioning that 17%-36% of all breast cancers happen in women aged under 40 (Thangjam et al., 2014; Wang et al., 2012). Nevertheless, there is currently little evidence concerning potential factors that contribute to the development of breast cancer in women younger than 40.

One potentially relevant factor in the development of breast cancer is obesity (Shapira, 2017). According to numerous studies, obesity is a risk factor in post-menopausal women (Neuhouser et al., 2015). For example, the results of a prospective study of a sample of 26,643 women in northern China performed by Guo et al. (2014) showed that there was a higher breast cancer incidence in obese postmenopausal women than in those whose weight was normal (adjusted HR = 1.97, CI of 95%: 1.01-3.82).

Another important factor in the development of breast cancer is family history. More specifically, Lancaster (2005) found that up to 18% of obese women diagnosed with breast cancer had a history of the disease in their families. According to Hu et al. (2021), Qiu et al. (2010) and Sheikh et al. (2015), mutations in the BRCA-1 and BRCA-2 genes are responsible for the majority of the cases that respond to a family pattern of breast cancer inheritance.

The relationship between female obesity and high serum levels of certain hormones as one of the principal risk factors for breast cancer has been explored by recent studies (Press & Pharoah, 2010). In fact, Key et al. (2011) detected a statistically significant association

among high serum levels of estrogen in obese women and the early development of breast cancer in comparison to non-obese women. After menopause, obese women experience a rise in estrogen levels with levels 50-100% higher than women of normal weight (Li et al., 2011; May 2014; Yoshimoto et al., 2011). This signifies that obese postmenopausal women are at greater risk of developing a breast tumor. When this happens, tumor growth is more rapid because it is hormonal-dependent (Sourouni & Kiesel, 2021; Zhang et al., 2013). In this sense, Borghesan et al. (2016) concluded that obese postmenopausal women were 3.80 or 1.80 times more likely to develop breast cancer than non-obese postmenopausal women.

Still another factor that should be considered in the genesis and prevention of breast cancer is the maternal lactation period. Recent studies show that females who exercised breastfeeding are at substantially less risk of developing breast cancer (Duche et al., 2021; James et al., 2011; Poorolajal et al., 2021). Factors that could explain the protective effect of breastfeeding are the reduction of estrogen levels (Fortner et al., 2019). Accordingly, a lower prevalence of breast cancer was observed in those women who had breastfed their children for periods longer than twelve months. This indicates that there is an inverse relation between the duration of the lactation period and the risk of developing breast cancer (Chang-Claude et al., 2000), regardless of the weight status of the subject (Hartz & He, 2013). Despite these findings, there is still a certain disagreement on the protective role of breastfeeding against the development of breast cancer, especially in the case of morbidly obese women (Amadou et al., 2013; Grossmann et al., 2010).

Furthermore, the risk of developing cancer is high in the case of obese female smokers, especially those who began smoking at a young age, and who have continued smoking over a long period of time (Byrne et al., 2010; Pader et al., 2021; Reynolds 2013; Van Kruijsdijk et al.,

2013). Luo et al. (2011) studied a sample population of 79,990 women, 50-79 years of age, and found that obese post-menopausal women who were active smokers were at greater risk of developing breast cancer than non-obese post-menopausal women. In another study conducted by Gao et al. (2013) on a sample population of women (669 cases and 682 controls) in the province of Jiangsu (China), both active and passive smoking were found to be risk factors for developing breast cancer. Nonetheless, despite the results of these studies, there is no consensus as to whether these breast cancer factors affect non-obese, obese, and morbidly obese women to the same degree (Ballard-Barbash et al., 2010; Polednak 2008).

This study was aimed to determine the extent to which the variable, age at breast cancer diagnosis, was affected by the factors, weight status (i.e. obesity/non-obesity), smoking habits, length of maternal lactation period, and family history of breast cancer. A secondary objective was to identify a possible association among weight status (i.e. morbid obesity) and serum estrogen levels.

Materials and methods

Design

It was performed a retrospective study on each clinical history of participants.

Sample & setting

The clinical and medical records of 524 women aged 19 to 91 years old, who had been diagnosed and treated at a University Hospital in Granada (Spain) from December 2011 to December 2019, were consulted.

Data collection

The International Code of Medical Ethics officially-recognized by the World Medical

Association and the Declaration of Helsinki were strictly followed in our research. Data collection processes followed standard ethical guidelines. The access to the clinical records was possible after obtaining a written authorization signed by all the participants. Authorization for the study was also obtained from the University Hospital where the data were collected.

Important data such as age at breast cancer diagnosis and length of maternal lactation period were consulted in the medical records of each patient. A distinction was made between women (i) who had never breastfed (NP), (ii) who had breastfed for less than 3 months [PL<3], (iii) who had breastfed for 3 to 6 months [PL 3,6] or (iv) who had breastfed for longer than 6 months [PL>6]. Those who had never been pregnant were included in the group of women who had never breastfed.

Other relevant variables for which data were recorded were the following: (i) antecedents of cancer in first-degree relatives such as father, mother, and siblings; (ii) smoking habits (whether the woman was a smoker); (iii) estradiol levels (measured by a blood test during the first visit and just before diagnosis); (iv) obesity. In regard to obesity, it was necessary to assess the nutritional status of each patient. The subjects' weight, height, and body mass index were obtained from the data collected from their medical histories. Women were classified into non-obesity, obesity, or morbid obesity according to the standards of the World Health Organization. Consequently, non-obese women had body mass index (BMI) values of <30; obese woman had BMI values of ≥30; and morbidly obese woman had BMI values of ≥40.00 (World Health Organization 1998).

All of this information was included in a data collection protocol, which was elaborated and validated by the members of the research team. This instrument permitted the extraction and collection of relevant information from the medical records of the subjects and its

subsequent storage in a computer database.

Statistical analysis

The statistical significance of the factors considered was verified by using the ANOVA and T-tests. It was set up a conditional inference tree to obtain the strongest associations among the response variable and the factors. A conditional inference tree is a statistics-based approach method that generates a decision tree, based on significance tests. The result is a flowchart-like structure, in which each internal node represents a 'test' of an attribute. Each branch of the decision tree represents the outcome of the test, and each leaf node represents a class label (decision taken after computing all attributes). The paths from root to leaf represent classification rules. The statistical analysis was made with the R statistical software application, party package (Hothorn et al., 2006).

Results

Figure 1 shows the mean age at breast cancer diagnosis, depending on whether the women were affected by one or more variables considered in the study. The results obtained (see Figure 1, node 1) show that for the sample population, the average age at diagnosis was significantly lower for obese women. Moreover, the morbidly obese subjects (see Figure 1, node 9) had significantly higher serum estrogen levels ($p = 0.04$). In those cases, the mean age at cancer diagnosis was approximately 30 for those women with estrogen levels ≤ 74.9 ng/ml and 38 for women with estrogen levels > 74.9 ng/ml (nodes 10 and 11). However, non-morbidly obese women were diagnosed with breast cancer at a more advanced age as reflected in nodes 5, 6, 7, and 8 (see Figure 1).

Non-obese and non-morbidly obese women (see Figure 1, node 2), who were smokers,

were diagnosed with breast cancer at approximately 50 years of age (see node 8). This was a younger age of diagnosis than that of women who were non-smokers. The differences found were statistically significant ($p < 0.001$). Female non-smokers (node 3) who had not breastfed or who had breastfed for less than three months were diagnosed with breast cancer at approximately 60 years of age (node 7). There were statistically significant differences ($p=0.013$) between the two groups (see Figure 1). Finally, the women who breastfed for more than three months, and who had a family history of breast cancer (node 6) were diagnosed with the disease at an age of < 60 years. In contrast, women without a family history of breast cancer (node 5) were diagnosed at an age of approximately 70 years. The differences between the two groups were statistically significant ($p = 0.025$).

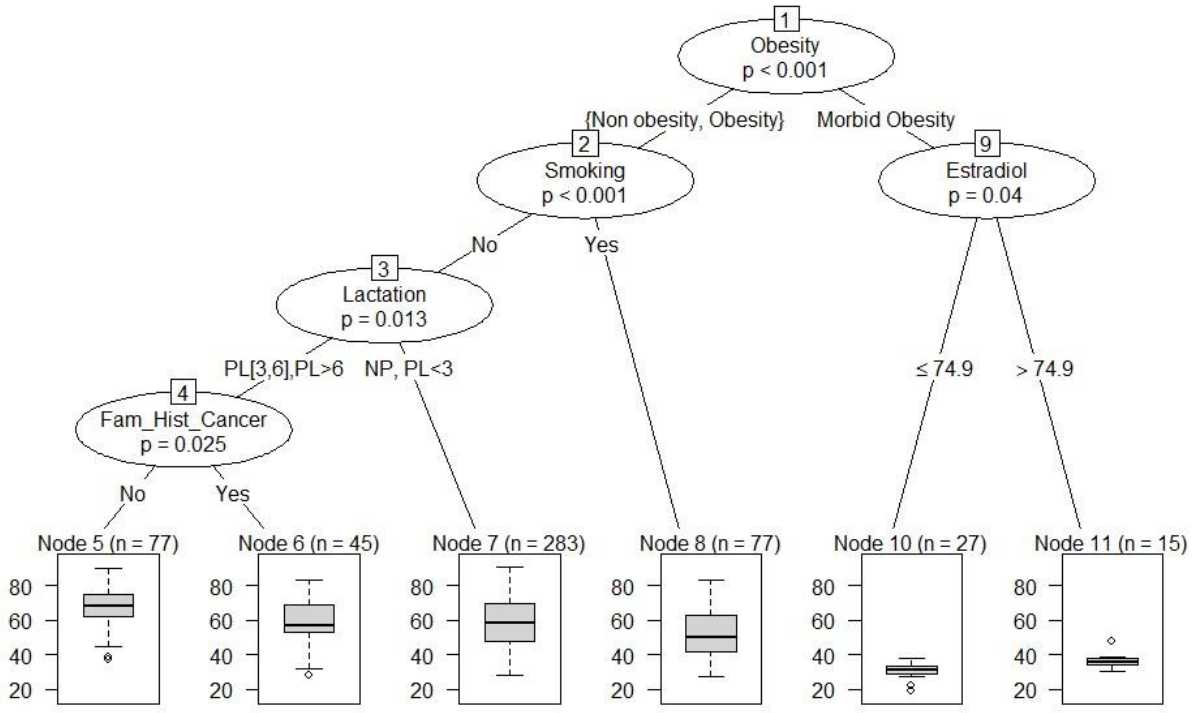

Figure 1. Conditional tree of age at diagnosis for the factors considered. [NP]: women who had never breastfed; [PL<3]: women who had breastfed for less than 3 months; [PL3-6]: women who

had breastfed for 3 to 6 months; [PL>6]: women who had breastfed for longer than 6 months; Node 1: Nutritional status; Node 2: Non-obese and obese women vs. smoking habits; Node 3: Non-obese and obese non-smokers vs. lactation; Node 4: Non-obese and obese non-smokers, who had breastfed for longer than 3 months vs family history of cancer; Node 5: Non-obese and obese non-smokers, who had breastfed for longer than 3 months without a family history of cancer; Node 6: Non-obese and obese non-smokers, who had breastfed for longer than 3 months with a family history of cancer; Node 7: Non-obese and obese non-smokers, who had breastfed for less than 3 months; Node 8: Non-obese and obese smokers; Node 9: Morbidly obese women vs. estradiol levels; Node10: Morbidly obese women with estrogen levels ≤ 74.9 ng/ml; Node 11: Morbidly obese women with estrogen levels > 74.9 ng/ml.

In the total sample population (see Table 1), nutritional status and smoking habits showed statistically significant differences ($p < 0.001$). In the case of non-obese and obese women, the average age at breast cancer diagnosis was approximately 60 years, whereas in the case of morbidly obese women, the average age at breast cancer diagnosis was younger than 40. Furthermore, women who were active smokers were diagnosed with breast cancer at an average age of approximately 50. In contrast, non-smokers were diagnosed at an average age of 58. In regard to the length of the maternal lactation period, no statistically significant differences were found ($p = 0.17$) in the average age at diagnosis. Nevertheless, there were statistically significant differences in the case of the variable, family history of cancer ($p = 0.05$). In other words, those women with family antecedents of breast cancer were diagnosed at an average age of 55.

Table 1. Statistical values for *t*-tests and ANOVA of age at diagnosis in relation to the factors considered.

	Age				
Factor	n	Mean	SD	F	p value
Obesity					
Non-obese	145	58.3	14.10	72.72	< 0.001
Obese	337	59.3	13.93		
Morbidly obese	42	32.9(*)	4.88		

	Age				
Factor	n	Mean	SD	*t*	p value
Smoking habits					
No	437	58.3	15.11	4.791	< 0.001
Yes	87	49.9	13.91		
Lactation period (months)					
NP, PL<3	383	55.8	15.18	-1.361	0.17
PL[3,6], PL>6	141	57.7	13.77		
Family history of breast cancer					
No	315	57.9	15.83	-1.813	0.05
Yes	209	55.0	14.20		

Note. Data are shown as mean ± SD.

[NP]: women who had never breastfed.

[PL<3]: women who had breastfed for less than 3 months.

[PL3,6]: women who had breastfed for 3 to 6 months.

[PL>6]: women who had breastfed for longer than 6 months.

(*) Nonhomogeneous group (Tukey's HSD post hoc test).

Discussion

The results obtained in this study show that among the morbidly obese women diagnosed with breast cancer, all except one of them were diagnosed before the age of 40. This finding is consistent with that of previous studies such as Wang et al. (2016), who reported a significant association of obesity with breast cancer in premenopausal women. The study performed by Castro-Espin et al. (2021) showed that premenopausal women consuming pro-inflammatory diets had higher risk of developing breast cancer. In this line, proper nutritional education and guidance by nursing professionals could help women to become aware of the advantages of a balanced diet. This would potentially contribute to reducing the risk of breast cancer.

Another important finding of this study was the confirmation of an association between the state of female morbid obesity combined with high blood levels of estrogen and a younger age at breast cancer diagnosis. These results coincide with the study of Paxton et al. (2013), who also found that obese women had higher estrogen levels and were diagnosed with breast cancer at an earlier age. Accordingly, the study performed by Tin Tin et al. (2020) reported that the highest levels of calculated free estradiol in premenopausal women were observed in those with the highest body mass index. Curiously, some authors have reported that obese women had a higher number of circulating adipose stromal cells than non-obese women. This is of great interest since these cells can raise serum estrogen levels and thus increase the risk of developing breast cancer at a young age (Baker et al., 2019; Ghosh et al., 2014).

In the case of normal weight or overweight (though not morbidly obese) female subjects, our study found that up to 16% had been smokers at some time during their lives. This percentage was lower than in other studies, such as the one carried out by Pader et al. (2021), in which the percentage of past smokers was 27%. These differences could stem from a greater awareness of the adverse effects of cigarette consumption for women suffering from cancer. In any case, a wide range of studies highlight the fact that smoking addiction is one of the main risk factors associated with the early development of breast cancer (Andersen et al., 2017; Li et al., 2016). Furthermore, in the case of non-morbidly obese women who were non-smokers, the mean age at breast cancer diagnosis was earlier in the case of those who had not breastfed their children or whose maternal lactation period was shorter than three months, which is indicative of a more unfavorable prognosis (Nafissi et al., 2018). This result partially coincides with Wang et al. (2020), who studied 3792 female breast cancer patients aged 20-70 years and found that among the young women who had not breastfed their children had a higher risk of developing a breast tumor. In the case of those women whose maternal lactation period was longer than three months, the mean age at breast cancer diagnosis was much later, which is in agreement with the previous reported protective effect of breastfeeding against breast cancer (American Cancer Society, 2019; Chowdhury et al., 2015). In fact, the length of the breastfeeding period in the case of non-morbidly obese women, who were non-smokers, was found to be proportional to the age at which breast cancer was diagnosed. The results of our study revealed that a family history of breast cancer could also lead to the development of breast cancer at an early age. As suggested by González-Jiménez et al. (2014), a family history of breast cancer is an important factor to be considered since it can even reduce the protective effect of maternal lactation for breast cancer. Our results confirmed this hypothesis since those subjects who had breastfed for longer than three

months and who had no family history of breast cancer were diagnosed with breast cancer at a more advanced age. Nevertheless, it is also true that despite existing evidence on the protection afforded by maternal lactation against breast cancer, some studies show no clear effects of breastfeeding on breast cancer incidence (Alsolami et al., 2019; Baset et al., 2021). For this reason, more in-depth studies and larger population samples are needed in order to investigate and possibly confirm the potential influence of factors, such as obesity or breastfeeding in the development of female breast cancer.

According to Hing et al. (2021), health talks at hospitals on breast cancer screening and treatment among healthcare professionals not only could help them in improving their knowledge and attitudes on this topic, but also in their actions focused on preventing breast cancer. Accordingly, nurses, as health educators, should foment healthy life styles and make women aware of the important role of a balanced diet in the prevention of obesity. Moreover, as another means of prevention breast cancer, especially if it is considered the scarce awareness of the breastfeeding protective effects on breast cancer (Hoyt-Austin et al., 2020; Sly et al., 2020), nursing professionals should also encourage women to breastfeed their children for as long as possible and avoid the consumption of harmful, addictive toxins, such those found in cigarettes (Lee et al., 2014)

Breast cancer risk factors from patient medical records are a limitation of great importance associated with retrospective chart review studies and can endanger the credibility of the research results. However, most retrospective chart review studies do not discuss medical records deficiencies or the methods implemented to lessen these limitations (Yawn & Wollan, 2005; Gregory & Radovinsky, 2012). By paying special attention to strategic methods, future studies can confirm the validity of the methods implemented and thus enhance the credibility of

the results generated from medical record data. Another limitation of our study was that given the number of medical histories analyzed and the number of simultaneous factors considered, it was not possible to analyze the data with a complete regression model, such as the General Linear Model, which is generally used to obtain the interaction effects between factors. This is particularly evident in the small number of women in the morbidly obese group. This means that the results of the present study should be interpreted with caution. Finally, our hormone study was limited to estradiol serum levels and did not include estrone and estriol serum values.

Conclusions

Our study has clarifying findings on certain factors such as morbid obesity, lactation period or smoking affect to breast cancer onset. Our results demonstrate that non-morbidly obese subjects who did not smoke and who had breastfed their children for longer than three months, on average, were diagnosed with breast cancer at a more advanced age. This result seems to indicate the potentially effect of maternal lactation in this subgroup of our sample population. Therefore, the involvement of healthcare and nursing professionals in the prevention of breast cancer necessarily includes the promotion breastfeeding, especially for periods of longer than six months as the optimal way to prevent the breast cancer.

Acknowledgements

The authors wish to thank the Saint Cecilio University Hospital of Granada for its support and for access to medical records.

Conflict of interests

The authors declare no conflicts of interest.

Funding Statement:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

EG-J conceived and designed the study; PAG analyzed the data; JS-R and ÁF-A collected the data; EG-J, JS-R and ÁF-A wrote the paper. All authors read and approved the final manuscript.

References

Alsolami, F. J., Azzeh, F. S., Ghafouri, K. J., Ghaith, M. M., Almaimani, R. A., Almasmoum, H. A., Abdulal, R. H., Abdulaal, W. H., Jazar, A. S., & Tashtoush, S. H. (2019). Determinants of breast cancer in Saudi women from Makkah region: a case-control study (breast cancer risk factors among Saudi women). *BMC Public Health, 19*(1), 1554. https://doi.org/10.1186/s12889-019-7942-3

Amadou, A., Hainaut, P., & Romieu, I. (2013). Role of obesity in the risk of breast cancer: lessons from anthropometry. *Journal of Oncology, 2013*, 906495. https://dx.doi.org/10.1155%2F2013%2F906495

American Cancer Society. (2019). Breast Cancer Facts & Figures 2019-2020. Atlanta: American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf

Andersen, Z. J., Jørgensen, J. T., Grøn, R., Brauner, E. V., & Lynge, E. (2017). Active smoking and risk of breast cancer in a Danish nurse cohort study. *BMC Cancer, 17*(1), 556. https://doi.org/10.1186/s12885-017-3546-4

Baker, H. A., Fabian, C. J., Hastings, R. C., Dixon, D. A., Nydegger, J. L., Phillips, T. A., Powers, K. R., & Kimler, B. F. (2019). Circulating adipose stromal cells as a response biomarker in phase II energy balance trials of obese breast cancer survivors and high-risk women. *Breast Cancer Research and Treatment, 176*(2), 387–394. https://doi.org/10.1007/s10549-019-05251-7

Ballard-Barbash, R., Berrigan, D., Potischman, N., & Dowling, E. (2010). Obesity and cancer epidemiology. In Berger NA (Eds.), *Cancer and Energy Balance, Epidemiology and Overview* (pp. 1-44). New York, USA: New York Springer-Verlag

Baset, Z., Abdul-Ghafar, J., Parpio, Y. N., & Haidary, A. M. (2021). Risk factors of breast cancer among patients in a tertiary care hospitals in Afghanistan: a case control study. *BMC Cancer*, *21*(1), 71. https://doi.org/10.1186/s12885-021-07798-5

Borghesan, D. H. P., Agnolo, C. M. D., Gravena, A. A. F., Demitto, M. de O., Lopes, T. C. R., Carvalho, M. D., & Pelloso, S. M. (2016). Risk Factors for Breast Cancer in Postmenopausal Women in Brazil. *Asian Pacific Journal of Cancer Prevention, 17*(7), 3587-3593.

Byrne, M. M., Davila, E. P., Zhao, W., Parker, D., Hooper, M. W., Caban-Martinez, A., Dietz, N., Huang, Y., Messiah, A., & Lee, D. J. (2010). Cancer screening behaviors among smokers and non-smokers. *Cancer Epidemiology*, *34*(5), 611-617. https://doi.org/10.1016/j.canep.2010.06.017

Castro-Espin, C., Agudo, A., Bonet, C., Katzke, V., Turzanski-Fortner, R., Aleksandrova, K., Schulze, M. B., Tjønneland, A., Dahm, C. C., Quirós, J.-R., Sánchez, M.-J., Amiano, P., Chirlaque, M.-D., Ardanaz, E., Masala, G., Sieri, S., Tumino, R., Sacerdote, C., Panico, S., … Jakszyn, P. (2021). Inflammatory potential of the diet and risk of breast cancer in the

European Investigation into Cancer and Nutrition (EPIC) study. *European Journal of Epidemiology*, *36*(9), 953–964. https://doi.org/10.1007/s10654-021-00772-2

Chang-Claude, J., Eby, N., Kiechle, M., Bastert, G., & Becher, H. (2000). Breastfeeding and breast cancer risk by age 50 among women in Germany. *Cancer Causes & Control: CCC*, *11*(8), 687-695. https://doi.org/10.1023/a:1008907901087

Chowdhury, R., Sinha, B., Sankar, M. J., Taneja, S., Bhandari, N., Rollins, N., Bahl, R., & Martines, J. (2015). Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. *Acta Paediatrica, 104*(467), 96–113. https://doi.org/10.1111/apa.13102

Duche, H., Tsegay, A. T., & Tamirat, K. S. (2021). Identifying risk factors of breast cancer among women attending selected hospitals of Addis Ababa city: Hospital-based unmatched case-control study. *Breast Cancer (Dove Medical Press), 13*, 189-197. https://doi.org/10.2147/bctt.s293867

Dudarev, A. A., Chupakhin, V. S., & Odland, J. Ø. (2013). Cancer incidence and mortality in Chukotka, 1997-2010. *International Journal of Circumpolar Health*, *72*, 20470. https://doi.org/10.3402/ijch.v72i0.20470

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, E., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*, *136*(5), E359–E386. https://doi.org/10.1002/ijc.29210

Fortner, R. T., Sisti, J., Chai, B., Collins, L. C., Rosner, B., Hankinson, S. E., Tamimi, R. M., Eliassen, A. H. (2019). Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. *Breast Cancer*

Research: BCR, *21*(1), 40. https://doi.org/10.1186/s13058-019-1119-y

Gao, C.-M., Ding, J.-H., Li, S.-P., Liu, Y.-T., Qian, Y., Chang, Y., Tang, J.-H., & Tajima, K. (2013). Active and passive smoking, and alcohol drinking and breast cancer risk in Chinese women. *Asian Pacific Journal of Cancer Prevention*, *14*(2), 993-996. https://doi.org/10.7314/apjcp.2013.14.2.993

Ghosh, S., Hughes, D., Parma, D. L., Ramirez, A., & Li, R. (2014). Association of obesity and circulating adipose stromal cells among breast cancer survivors. *Molecular Biology Reports*, *41(5)*, 2907-2916. https://doi.org/10.1007/s11033-014-3146-1

González-Jiménez, E., García, P. A., Aguilar, M. J., Padilla, C. A., & Álvarez, J. (2014). Breastfeeding and the prevention of breast cancer: a retrospective review of clinical histories. *Journal of Clinical Nursing*, *23*(17-18), 2397-2403. https://doi.org/10.1111/jocn.12368

Gregory, K. E., & Radovinsky, L. (2012). Research strategies that result in optimal data collection from the patient medical record. *Applied Nursing Research: ANR*, *25*(2), 108–116. https://doi.org/10.1016/j.apnr.2010.02.004

Grossmann, M. E., Ray, A., Nkhata, K. J., Malakhov, D. A., Rogozina, O. P., Dogan, S., & Cleary, M. P. (2010). Obesity and breast cancer: status of leptin and adiponectin in pathological processes. *Cancer Metastasis Reviews*, *29*(4), 641-653. https://doi.org/10.1007/s10555-010-9252-1

Guo, L., Li, N., Wang, G., Su, K., Li, F., Yang, L., Ren, J., Chang, S., Chen, S., Wu, S., He, J., & Dai, M. (2014). Body mass index and cancer incidence: a prospective cohort study in northern China. *Zhonghua Liu Xing Bing Xue Za Zhi*, *35*(3), 231-236.

Hartz, A. J., & He, T. (2013). Cohort study of risk factors for breast cancer in post menopausal women. *Epidemiology and Health, 35*, e2013003. https://doi.org/10.4178/epih/e2013003

Hing, J. J. X., Lee, W. P., Chua, Y. N. S., Tan, P. T., Mok, C. W., Sudhakar, S. S., Seah, C. M., & Tan, S.-M. (2021). Impact of health talks on knowledge, attitudes and perception of breast cancer screening and treatment amongst healthcare staff by a breast surgical unit in a public healthcare institution: a cross-sectional study. *BMC Women's Health, 21*(1), 308. https://doi.org/10.1186/s12905-021-01424-z

Holmberg, E., Anderson, H., Lundell, M., & Karlsson, P. (2005). The impact of reproductive factors on breast cancer risk the feasibility of using Swedish population-based registers to account for the effect of confounding in cohort studies. *Cancer Causes & Control: CCC, 16*(3), 235–243. https://doi.org/10.1007/s10552-004-3363-3

Hothorn, T., Hornik, K., & Zeileis, A. (2006). Unbiased Recursive Partitioning: A conditional inference framework. *Journal of Computational and Graphical Statistics, 15*(3), 651-674. https://doi.org/10.1198/106186006X133933

Hoyt-Austin, A., Dove, M. S., Abrahão, R., Kair, L. R., & Schwarz, E. B. (2020). Awareness That Breastfeeding Reduces Breast Cancer Risk: 2015-2017 National Survey of Family Growth. *Obstetrics and Gynecology, 136*(6), 1154–1156. https://doi.org/10.1097/AOG.0000000000004162

Hu, C., Hart, S. N., Gnanaolivu, R., Huang, H., Lee, K. Y., Na, J., Gao, C., Lilyquist, J., Yadav, S., Boddicker, N. J., Samara, R., Klebba, J., Ambrosone, C. B., Anton-Culver, H., Auer, P., Bandera, E. V., Bernstein, L., Bertrand, K. A., Burnside, E. S., …Couch, F. J. (2021). A population-based study of genes previously implicated in breast cancer. *The New England*

Journal of Medicine, 384(5), 440-451. https://doi.org/10.1056/nejmoa2005936

James, R. E., Lukanova, A., Dossus, L., Becker, S., Rinaldi, S., Tjønneland, A., Olsen, A., Overvad, K., Mesrine, S., Engel, P., Clavel-Chapelon, F., Chang-Claude, J., Vrieling, A., Boeing, H., Schütze, M., Trichopoulou, A., Lagiou, P., Trichopoulos, D., Palli, D., …Kaaks, R. (2011). Postmenopausal serum sex steroids and risk of hormone receptor –positive and –negative breast cancer: a nested case-control study. *Cancer Prevention Research (Philadelphia, Pa.), 4*(10), 1626-1635. https://doi.org/10.1158/1940-6207.capr-11-0090

Key, T. J., Appleby, P. N., Reeves, G. K., Roddam, A. W., Helzlsouer, K. J., Alberg, A. J., Rollison, D. E., Dorgan, J. F., Brinton, L. A., Overvad, K., Kaaks, R., Trichopoulou, A., Clavel-Chapelon, F., Panico, S., Duell, E. J., Peeters, P. H. M., Rinaldi, S., Fentiman, I. S., Dowsett, M., …Strickler, H. D. (2011). Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *British Journal of Cancer, 105*(5), 709-722. https://doi.org/10.1038/bjc.2011.254

Lancaster, D. R. (2005). Coping with appraised breast cancer risk among women with family histories of breast cancer. *Research in Nursing & Health, 28*(2), 144–158. https://doi.org/10.1002/nur.20066

Lee, H., Li, J.-Y., Fan, J.-H., Li, J., Huang, R., Zhang, B.-N., Zhang, B., Yang, H.-J., Xie, X.-M., Tang, Z.-H., Li, H., He, J.-J., Wang, Q., Huang, Y., Qiao, Y.-L., & Pang, Y. (2014). Risk factors for breast cancer among Chinese women: a 10-year nationwide multicenter cross-sectional study. *Journal of Epidemiology, 24*(1), 67-76. https://doi.org/10.2188/jea.je20120217

Li, P., Huang, J., Wu, H., Fu, C., Li, Y., & Qiu, J. (2016). Impact of lifestyle and psychological

stress on the development of early onset breast cancer. *Medicine, 95*(50), e5529. https://doi.org/10.1097/MD.0000000000005529

Li, X.-J., Wei, B., Chen, H.-J., Zhang, Z., Zhang, H.-Y., & Bu, H. (2011). Heat-induced antigen retrieval in immunohistochemistry for estrogen and progesterone receptors in breast cancer tissues. *Zhonghua Bing Li Xue Za Zhi, 40*(6), 406-408.

Luo, J., Margolis, K. L., Wactawski-Wende, J., Horn, K., Messina, C., Stefanick, M. L., Tindle, H. A., Tong, E., & Rohan, T. E. (2011). Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. *The BMJ, 342*, D1016. https://doi.org/10.1136/bmj.d1016

May, F. E. B. (2014). Novel drugs that target the estrogen-related receptor alpha: their therapeutic potential in breast cancer. *Cancer Management and Research, 23*(6), 225-252. https://dx.doi.org/10.2147%2FCMAR.S35024

Nafissi, N., Faraji, M., Hosseini, M., Shojaee, L., Ziaei, F., Akbari, M. E., & Mousavie, S. H. (2018). Relationships between Reproductive Risk Factors for Breast Cancer and Tumor Molecular Subtypes. *Asian Pacific Journal of Cancer Prevention: APJCP, 19*(7), 1767–1770. https://doi.org/10.22034/APJCP.2018.19.7.1767

Neuhouser, M. L., Aragaki, A. K., Prentice, R. L., Manson, J. E., Chlebowski, R., Carty, C. L., Ochs-Balcom, H. M., Thomson, C. A., Caan, B. J., Tinker, L. F., Urrutia, R. P., Knudtson, J., & Anderson, G. L. (2015). Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Oncology, 1*(5), 611-621. https://doi.org/10.1001/jamaoncol.2015.1546

Pader, J., Basmadjian, R. B., O'Sullivan, D. E., Mealey, N. E., Ruan, Y., Friedenreich, C., Murphy, R., Wang, E., Quan, M. L., & Brenner, D. R. (2021). Examining the etiology of early-onset breast cancer in the Canadian Partnership for Tomorrow's Health (CanPath). *Cancer Causes & Control, 32*(10), 1117–1128. https://doi.org/10.1007/s10552-021-01460-y

Paxton, R. J., King, D. W., Garcia-Prieto, C., Connors, S. K., Hernandez, M., Gor, B. J., & Jones, L. A. et al (2013). Associations between body size and serum estradiol and sex hormone-binding globulin levels in premenopausal African American women. *The Journal of Clinical Endocrinology and Metabolism, 98*(3), E485-E490. https://doi.org/10.1210/jc.2012-2782

Polednak, A. P. (2008). Estimating the number of U.S. incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. *Cancer Detection and Prevention, 32*(3), 190-199. https://doi.org/10.1016/j.cdp.2008.08.004

Poorolajal, J., Heidarimoghis, F., Karami, M., Cheraghi, Z., Gohari-Ensaf, F., Shahbazi, F., Zareie, B., Ameri, P., & Sahraei, F. (2021). Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. *Journal of Research in Health Sciences, 21*(3), e00520–e00520. https://doi.org/10.34172/jrhs.2021.57

Press, D. J., & Pharoah, P. (2010). Risk Factors for Breast Cancer: A reanalysis of two case-control studies from 1926 and 1931. *Epidemiology, 21*(4), 566–572. https://doi.org/10.1097/ede.0b013e3181e08eb3

Qiu, L.-X., Yao, L., Xue, K., Zhang, J., Mao, C., Chen, B., Zhan, P., Yuan, H., & Hu, X.-C. (2010). BRCA2 N372H polymorphism and breast cancer susceptibility: a meta-analysis involving 44.903 subjects. *Breast Cancer Research and Treatment, 123*(2), 487–490.

https://doi.org/10.1007/s10549-010-0767-5

Reynolds, P. (2013). Smoking and breast cancer. *Journal of Mammary Gland Biology and Neoplasia, 18*(1), 15-23. https://doi.org/10.1007/s10911-012-9269-x

Shapira, N. (2017). The potential contribution of dietary factors to breast cancer prevention. *European Journal of Cancer Prevention, 26*(5), 385-395. https://doi.org/10.1097/cej.0000000000000406

Sheikh, A., Hussain, S. A., Ghori, Q., Naeem, N., Fazil, A., Giri, S., Sathian, B., Mainali, P., & Tamimi, D. M. A. (2015). The spectrum of genetic mutations in breast cancer. *Asian Pacific Journal of Cancer Prevention, 16*(6), 2177-2185. https://doi.org/10.7314/apjcp.2015.16.6.2177

Siegel, R. L., Miller, K. D., & Jemal, A. (2016). Cancer Statistics, 2016. *CA: A Cancer Journal for Clinicians, 66*(1), 7-30. https://doi.org/10.3322/caac.21332

Sly, J. R., Miller, S. J., Thelemaque, L., Yazdanie, F., Sperling, R., Sasan, F., Howell, E. A., Loudon, H., & Jandorf, L. (2020). Knowledge of the Relationship Between Breastfeeding and Breast Cancer Risk Among Racial and Ethnic Minority Women. *Journal of Cancer Education, 35*(6), 1193–1196. https://doi.org/10.1007/s13187-019-01580-9

Sourouni, M., & Kiesel, L. (2021). Hormone replacement therapy after gynaecological malignancies: a review article. *Geburtshilfe und Frauenheilkunde, 81*(5), 549-554. https://dx.doi.org/10.1055%2Fa-1390-4353

Thangjam, S., Laishram, R. S., & Debnath, K. (2014). Breast carcinoma in young females below the age of 40 years: A histopathological perspective. *South Asian Journal of Cancer, 3*(2), 97-100. https://dx.doi.org/10.4103%2F2278-330X.130441

Tin Tin, S., Reeves, G. K., & Key, T. J. (2020). Body size and composition, physical activity and sedentary time in relation to endogenous hormones in premenopausal and postmenopausal women: Findings from the UK Biobank. *International Journal of Cancer, 147*(8), 2101–2115. https://doi.org/10.1002/ijc.33010

Van Kruijsdijk, R. C. M., Van der Graaf, Y., Peeters, P. H. M., Visseren, F. L. J., & Second Manifestations of arterial disease (SMART) study group. (2013). Cancer risk in patients with manifest vascular disease: effects of smoking, obesity, and metabolic syndrome. *Cancer Epidemiology, Biomarkers & Prevention, 22*(7), 1267-1277. https://doi.org/10.1158/1055-9965.epi-13-0090

Wang, X., Li, L., Gao, J., Liu, J., Guo, M., Liu, L., Wang, W., Wang, J., Xing, Z., Yu, Z., & Wang, X. (2016). The association between body size and breast cancer in Han women in Northern and Eastern China. *The Oncologist,* 2016, *21*(11), 1362-1368. https://dx.doi.org/10.1634%2Ftheoncologist.2016-0147

Wang, J. M., Wang, J., Zhao, H. G., Liu, T. T., & Wang, F. Y. (2020). Reproductive Risk Factors Associated with Breast Cancer Molecular Subtypes among Young Women in Northern China. *BioMed Research International, 2020*, 5931529. https://doi.org/10.1155/2020/5931529

Wang, Y. C., Wei, L. J., Liu, J. T., Li, S. X., & Wang, Q. S. (2012). Comparison of cancer incidence between China and the USA. *Cancer Biology & Medicine, 9*(2), 128-132. https://dx.doi.org/10.3969%2Fj.issn.2095-3941.2012.02.009

World Health Organization (WHO). (2000). *Obesity: preventing and managing the global epidemic: report of a WHO consultation* (NLM Classification: WD 710). Geneva:

Switzerland.

Yawn, B. P., & Wollan, P. (2005). Interrater reliability: Completing the methods description in medical records review studies. *American Journal of Epidemiology*, *161*(10), 974–977. https://doi.org/10.1093/aje/kwi122

Yoshimoto, N., Nishiyama, T., Toyama, T., Takahashi, S., Shiraki, N., Sugiura, H., Endo, Y., Iwasa, M., Fujii, Y., & Yamashita, H. (2011). Genetic and environmental predictors, endogenous, hormones and growth factors, and risk of estrogen receptor positive breast cancer in Japanese women. *Cancer Science*, *102*(11), 2065-2072. https://doi.org/10.1111/j.1349-7006.2011.02047.x

Zhang, X., Tworoger, S. S., Eliassen, A. H., & Hankinson, S. E. (2013). Post menopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. *Breast Cancer Research and Treatment*, *137*(3), 883-892. https://doi.org/10.1007/s10549-012-2391-z