The Impact of the Characteristics of Exercise on The Risk of Breast Cancer Instructions

Andriani Vouxinou1, Georgios Iatrakis1, Stefanos Zervoudis1, 2, Maria Dagla1, Eirini Orovou1, Ermini Palaska1, Angeliki Sarella1, Evangelia Antoniou1

ABSTRACT
Background: Exercise seems to protect from breast cancer (BC) and this protection is likely mediated through weight control during menopause. Considering that night work is associated with higher risk for BC. Objective: The aim of this study was to examine the possible relation of BC risk to daytime or nighttime hours of exercise. Methods: The material was taken from primary elements of a doctoral thesis at the Department of Midwifery, University of West Attica that examines the impact of the characteristics of exercising on BC. The data were obtained from relevant questionnaires filled in at a big private hospital, following a relevant permit of the scientific committee, and adjusted Google Forms, ensuring anonymity. Results: Almost 3 times more women without a history of BC were exclusively exercising during the daytime compared to the ones with a history of BC who were exclusively exercising during the nighttime (40 vs 15). On the contrary, a smaller number of women without a history of BC were exclusively exercising during the nighttime compared to the ones with a history of BC who were exclusively exercising during the nighttime (17 vs 20) (odds ratio >3 with a confidence interval >1 to >7.5 and p<0.05). Conclusion: It seems that the protective impact of exercising on BC is mitigated when the exercise is performed exclusively during night hours. Keywords: breast cancer; exercise; risk factor; exercising during the nighttime; exercising during the daytime.

1. BACKGROUND
Obesity in postmenopausal women is included in the major factors that have been consistently associated with a higher risk of breast cancer from both European (1) and US (2) data. On the other hand, exercise seems to protect from breast cancer. This protection is likely mediated through weight control and hormonal influences such as impairing serum insulin levels (3) and estrogens. When exercising, metabolism increases (4), the cardiovascular function accelerates (5), and blood parameters (6) seem to be affected. The endocrine system seems to play an important role in those changes (7). It would be logical, thus, for someone to assume that exercise plays an important role in hormone-dependent conditions, such as breast cancer (BC).

Indeed, exercising is included in the factors that can lower the risk for BC (8-10). However, the causal pathway underlying the association between exercise and cancer risk reduction is less clear (11). Furthermore, increased estrogen levels and increased bone density seem to raise the risk of BC (9). Actually, exercise is effective in improving estradiol levels of postmenopausal osteoporotic females and the efficacy of anaerobic exercise was found to be more potent on estradiol levels than that related to aerobic exercise (12). Still, besides the above mentioned impacts, exercising has a possible primary protective impact on certain cancers or precancer lesions, such as BC, endometrial hyperplasia, endometrial cancer, colon cancer and prostate cancer (13-16) and it seems also to protect from a possible recurrence and mortality (16, 17). Essentially, in experimental studies, exercise training prevented endometrial hyperplasia and biomarkers for endometrial cancer (18), an hormonally dependent cancer in humans, such as BC. It is noted that even the mildest type of exercise seems to be protective for BC (19). Gi-
ven that few women have included a systematic exercising regimen in their daily activities, the last observation, i.e. that even light exercise is enough to protect from BC, is very encouraging. Furthermore, a broad spectrum of studies described the relations of cancer treatment (as surgery and adjuvant therapy) and complications (as lymphedema) with exercise in breast cancer survivors (20-22).

Finally, it was hypothesized that exercise has protective effects against other hormonally dependent diseases characterized by inflammatory processes, such as endometriosis, since it increases cytokines with anti-inflammatory properties (23), hypothesis confirmed in experimental data (24).

2. OBJECTIVE

The aim of the study was to demonstrate the possible impact of the characteristics of the exercise on the risk for BC. The initial idea derived from the fact that night work is associated with higher risk for BC for workingwomen (25) due to the suppressive impact on melatonin levels in conditions of night work (26), although there is no agreement in all studies. Given this fact, possible suppression, of the above levels during night exercise (or any other mechanism) could possibly affect the more general benefit of exercising on BC.

3. MATERIAL AND METHODS

Please MS Word, following the instructions about preparing figures, tables and references presented herein. The material was taken from primary elements of a doctoral thesis at the Department of Midwifery, University of West Attica, and, inter alia, examines the impact of the characteristics of exercising (during the day or the night) on BC. Apart from the hours of exercise during the day or the night, the type of the exercise was also recorded, but these data have not been analyzed yet. The data were taken from a relevant questionnaire filled in at a big private hospital, following a relevant permit of the competent scientific committee, and adjusted Google Forms (total number: 300) for a predetermined time period, ensuring anonymity. The questionnaire included classic risk factors for breast cancer and factors related to exercise (Table 1). Initially, limited data were analyzed using the chi-square test to see if there was association between night exercise and the risk for BC. The odds-ratio calculation was used to estimate the strength of this relation. The second calculation was performed after introducing the data to the SPSS 20 (without the need for VPN activation) and then to the SPSS 26 (after activating the VPN with Tunnelblick and connecting with the University of the West Attica), when problems were detected in the reading of Greek fonts in the first edition. The results were confirmed with relevant software in a Mac environment where only the total number of the people belonging to each group was required and not the analytical recording of the data (per woman). Indicatively, the (subscription) MEDCALC software was used. Our research does not include laboratory measurements for the time being.

4. RESULTS

Headings should be capitalized (i.e. nouns, verbs, and all other words except articles, prepositions, and conjunctions should be set with an initial capital) and should be aligned to the left. Words joined by a hyphen are subject to a special rule. If the first word can stand alone, the second word should be capitalized. Despite the relevantly satisfactory number of women participating in the study, there was some difficulty in achieving the initial aim of the study, because quite a big percentage of the women did not exercise at all during the day or the night. However, skewness and kurtosis of available figures were shown a normal univariate distribution increasing the data strength (Table 2). Almost three times more women without a history of BC exclusively exercised during the day compared to the ones with a history of BC exclusively exercising during the day (40 vs 15) (Figure 1). On the contrary, a slightly smaller number of women without a history of BC exclusively exercised during the night compared to the ones with a history of BC who exclusively exercised during the night (17 vs 20) (Figure 2).

The statistical analysis of the sample showed that the odds ratio was almost three times higher (odds ratio >3

| Factors related to breast cancer risk | Factors possibly related to exercise | Exercise characteristics |
|------------------------------------|-------------------------------------|-------------------------|
| Family history of breast cancer | Current Weight | Time of day |
| History of breast biopsy | Weight in younger ages | Kind of exercise |
| Age | Weight gain during pregnancies | Duration of exercise |

Table 1. Indicative factors included in the questionnaire related to the risk of breast cancer and under investigation (3rd column) for the risk of breast cancer.

Figure 1. Almost three times more women without breast cancer exclusively exercised during the day.

Figure 2. Slightly higher number of women with breast cancer exclusively exercised during the night.
with a confidence interval $1 > 7.5$ and $p < 0.05$) although this seemed to mainly derive from the higher number of the healthy women without a history of BC exercising during non-night hours compared to the ones with a history of BC exercising during non-night hours. The coincidence of the SPSS results with the ones of MEDCALC was reflected up to the third decimal digit. Indicatively, the higher limit of the above confidence interval was 7.545 and 7.5456 in the SPSS and MEDCALC, respectively. The data estimation continues to a multifactorial analysis.

5. DISCUSSION

Exercising is included in a big group of factors that can affect the risk for BC (10) and other cancers. Although the exact mechanisms are not fully understood, some causal relations are obvious. Various studies have shown that certain types of exercise, such as aerobic exercise, can reduce the risk of breast cancer. Additionally, weight loss and maintenance through regular exercise may reduce the risk of breast cancer recurrence and death (39).

It is noted that the wide confidence interval of the results differs from the narrower corresponding intervals in a similar study. The coincidence of the SPSS results with the ones of MEDCALC was reflected up to the third decimal digit. Indicatively, the higher limit of the above confidence interval was 7.545 and 7.5456 in the SPSS and MEDCALC, respectively. The data estimation continues to a multifactorial analysis.

6. CONCLUSIONS

The protective impact of exercising on BC is possibly mitigated, when exclusively exercising during the night. Exclusively exercising during night hours may not act as a risk factor for BC increase.

In the procedure of further analyzing and expanding our data, some other factors related to exercise may impact the influence of the exercise to BC risk, such as the kind of exercise.

The endocrinology laboratory association and documentation of the epidemiological findings in similar trials of a bigger scale would be interesting in the future.

REFERENCES

1. Lahnmann, PH.; Hoffmann, K.; Allen, N.; van Gils, CH.; Khaw, KT.; Tehard, B.; et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Maastricht study. Eur J Cancer Prev 2002; 11: 357-66.

Table 2. Indicative information for factors influencing the risk of breast cancer.

| Factor          | Range   | Minimum | Maximum | Mean  | Standard deviation | Skewness | Kurtosis |
|-----------------|---------|---------|---------|-------|--------------------|----------|----------|
| Age (years)     | 57      | 25      | 82      | 52.9  | 12.7               | 0.3      | -0.5     |
| Weight (kg)     | 47      | 48      | 95      | 68.9  | 10.9               | 0.1      | -0.5     |
| Height (cm)     | 18      | 150     | 178     | 164.3 | 6.2                | 0.2      | -0.9     |

Acknowledgements: We would like to express our gratitude for C. Tsibos, Professor Emeritus, Department of Statistics & Insurance Science—University of Piraeus (Greece), whose support has been invaluable throughout this study.

Patient Consent Form: All participants were informed and agreed to participate in the study.

Authors contribution: conceptualization, A.V., G.I.; methodology, A.V., G.I., E.A.; software, A.V., G.I., E.O.; validation, E.A., M.D., A.S., E.P., S.Z.; formal analysis, A.V., G.I., E.A.; investigation, A.V., E.A.; resources, E.A., A.S., E.P., S.Z.; data curation, E.A., A.S., E.P., S.Z.; writing—original draft preparation, A.V., G.I., E.O.; writing—review and editing, A.V., G.I., E.A., E.O.; visualization, A.V., G.I., E.O.; supervision, E.A., M.D.; project administration, E.A., M.D.

Conflict of interest: The authors declare no conflict of interest.

Financial support and sponsorship: This research received no external funding.
The Impact of the Characteristics of Exercise on The Risk of Breast Cancer Instructions

5. Hellsten Y, Nyberg M. Cardiovascular Adaptations to Exercise Training. J Appl Physiol. 2009 Jan; 106(1): 62–74.

10. Alegre MM, Knowles MH, Robison RA, O’Neill KL. Mechanics behind breast cancer prevention–focus on obesity, exercise and dietary fat. Asian J Sports Med. 2013; 4(4): 220–227.

15. Factors that modify breast cancer risk in women–UpToDate [Internet]. [cited 2020 Mar 12]. Available from: https://www.uptodate.com/contents/factors-modify-breast-cancer-risk-in-women.

20. Wilson DJ. Exercise for the Patient after Breast Cancer Surgery. Semin Oncol Nurs. 2017 Feb; 33(1): 98–105.

21. Nelson NL. Breast Cancer-Related Lymphedema and Resistance Exercise: A Systematic Review. J Strength Cond Res. 2016 Sep; 30(9): 2656–2665.

22. van V, Ph P, M V, van der W, Am M. Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: A meta-analysis. Maturitas [Internet]. 2015 Dec 28 [cited 2021 Apr 24]; 85: 104–111. Available from: https://www.sciencedirect.com/science/article/pii/S0378512215004230.

23. Bonocher CM, Montenegro ML, Rosa e Silva JC, Ferriani RA, Meola J. Endometriosis and physical exercises: a systematic review. Reprod Biol Endocrinol [Internet]. 2014 Jan 6 [cited 2021 Apr 24];12:4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC395811/.

24. Montenegro ML, Bonocher CM, Meola J, Portella RL, Ribeiro-Silva A, Brunaldi MO, et al. Effect of Physical Exercise on Endometriosis Experimentally Induced in Rats. Reprod Sci. 2019 Jun; 26(6): 785–795.

25. Wang F, Yeung KL, Chan WC, Kwok CCH, Leung SL, Wu C, et al. A meta-analysis on dose-response relationship between shift work and the risk of breast cancer. Ann Oncol. 2015 Nov 24; (11): 2724–2732.

26. Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. J Natl Cancer Inst. 2005 Jul 20; 97(14): 1084–1087.

27. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. J Gastroenterol Hepatol. 2013 Dec;28 Suppl 4: 49–55.

28. Nelson RJ, Chibeir S. Dark matters: effects of light at night on metabolism. Proc Nutr Soc. 2018 Aug; 77(3): 223–229.

29. Sun K, Xie Y, Zhao N, Li Z. A case-control study of the relationship between visceral fat and development of uterine fibroids. Exp Ther Med [Internet]. 2019 Jul [cited 2021 Apr 24]; 18(1): 404–410. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566109/

30. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. Eur J Cancer. 2012 Jul; 48(11): 1722–1729.

31. Gleeson PB, Protas EJ, LeBlanc AD, Schneider VS, Evans HJ. Effects of weight lifting on bone mineral density in premenopausal women. J Bone Miner Res. 1990 Feb; 5(2): 153–158.

32. Karimi MT. The influence of walking with an orthosis on bone mineral density by determination of the absolute values of the loads applied on the limb. Australas Phys Eng Sci Med [Internet]. 2012 Mar 1 [cited 2021 Apr 24]; 35(1): 55–61. Available from: https://doi.org/10.1007/s13246-011-0121-1

33. Mussolino ME, Looker AC, Orwell ES. Jogging and bone mineral density in men: results from NHANES III. Am J Public Health. 2001 Jul; 91(7): 1056–1059.

34. Ermin K, Owens S, Ford MA, Bass M. Bone Mineral Density of Adolescent Female Tennis Players and Nontennis Players. J Osteoporos [Internet]. 2012 [cited 2021 Apr 24]; 2012. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3591715/.

35. Nichols DL, Sanborn CF, Essery EV. Bone density and young athletic women. An update. Sports Med. 2007; 37(11): 1001–1014.

36. Qu X, Zhang X, Qin A, Liu G, Zhao Z, Hao Y, et al. Bone mineral density and risk of breast cancer in postmenopausal women. Breast Cancer Res Treat. 2015 Feb; 158(1): 261–271.

37. Chen Z, Arendell L, Acklin M, Cauley J, Lewis CE, Chlebowski R. HIP Bone Density Predicts Breast Cancer Risk Independently of Gail Score-Results From the Women’s Health Initiative. Cancer [Internet]. 2008 Sep 1 [cited 2021 Apr 24];113(5):907–15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2909006/.

38. Kubatka P, Zubar P, Busseberg D, Koon TK, Adamek M, Petrovic D, et al. Melatonin and breast cancer: Evidences from preclinical and human studies. Crit Rev Oncol Hematol. 2018 Feb; 122: 135–145.

39. Irwin ML. Physical activity interventions for cancer survivors. Br J Sports Med. 2009 Jan; 43(1): 52–58.