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Editorial

Cancer Prevention Research

Combining Variables for Cancer Risk Estimation: Is the Sum Better than the Parts?

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Abstract

Examining joint exposures of modifiable breast cancer risk factors may provide advantages over individual exposure–disease association analyses. Using the Healthy Lifestyle Index, Arthur and colleagues analyzed the joint impacts of diet, alcohol, smoking, physical activity, and obesity on breast cancer risk, and subtypes, in postmenopausal women enrolled in the Women's Health Initiative. The analysis provides data for population-attributable risk estimations and future prevention trials to target multiple risk factors. The public health messages for the individual risk factors remain unchanged, however, and it is still not clear whether improving one risk factor can counteract the adverse effects of another. *Cancer Prev Res; 11(6); 313–6. ©2018 AACR.*

See related article by Arthur et al., p. 317

Over the past half century, a large body of research has been conducted on modifiable lifestyle breast cancer risk factors. International agencies such as the World Cancer Research Fund/American Institute of Cancer Research have conducted systematic reviews and meta-analyses of the evidence and provided public health recommendations for breast cancer prevention (1). These recommendations have largely been based on observational epidemiologic research studies that have focused on individual risk factors that have examined confounding and effect modification by other individual factors. There has been relatively little investigation of combined risk factors for breast cancer from one study. Hence, the article by Arthur and colleagues (2) is a novel addition to the breast cancer risk factor literature.

Using the Healthy Lifestyle Index (HLI), Arthur and colleagues examined the joint effects of diet, alcohol intake, body mass index (kg/m^2), physical activity, and smoking on breast cancer risk in postmenopausal women enrolled in the Women's Health Initiative (WHI) study. They used data from over 130,000 women who were participants in either the WHI observational study or the clinical trial followed up from study initiation (1993–1998) to 2016. With over 8,100 women diagnosed with breast cancer, this study had sufficient statistical power to examine the association of the HLI on breast cancer risk. In addition, the WHI was recognized for the quality of the data collection and the local physician and central adjudication to ascertain all cancer cases and their stage and tumor characteristics. To date, only two other cohorts, the E3N (the French cohort study of teachers; ref. 3) and the European Prospective Investigation on Cancer (4) have examined the association between the HLI and breast cancer risk.

The study by Arthur and colleagues (2) found a 4% reduction in breast cancer risk with each unit decrease in the HLI score, which was equivalent to a 30% decreased risk when comparing those women in the highest versus lowest quintile. This reduction in risk was observed for all breast cancer patients irrespective of their nodal status, tumor grade, stage of disease, hormone therapy use, race/ethnicity, or family history of breast cancer, suggesting that these combined lifestyle factors have a universal impact on breast cancer risk. Reductions in risk were seen for estrogen receptor–positive (ER$^+$)/progesterone receptor–positive (PR$^+$) and HER2$^+$ breast cancers, but not for ER$^-$/PR$^-$ or ER$^+$/PR$^-$ cancers. These results were further strengthened by the findings that individual risk factors (other than diet score) that comprised the HLI score were also associated with reductions in breast cancer risk. Previous research has suggested that 25% to 30% of breast cancers can be attributable to modifiable factors (5); hence, this study provides additional evidence to support prior estimates.

Breast cancer risk stratification based on clinical, genetic, and reproductive variables has been used clinically for determining benefit and risk from screening and preventive treatments (6). It would be important to know whether the HLI score could add useful information to those risk stratification schemes.

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The advantage of this approach is that the combination of risk factor data provides a more comprehensive and realistic assessment of individual risks for breast cancer than separate analyses of individual risks. In so doing, patterns of lifestyle behaviors can be jointly considered when cancer prevention guidelines are created. Agencies such as the World Cancer Research Fund/American Institute of Cancer Research with their decennial publications on the scientific evidence for lifestyle factors and cancer prevention and survival have focused on individual risk factor recommendations. Indeed, other investigators have examined how adherence to these guidelines is associated with cancer risk (7), but no previous studies of the association between HLI and breast cancer risk have examined the effects within subgroups of patients defined by tumor nodal status, grade, and stage. The finding that the risk reduction occurs across most subgroups reinforces the importance of healthy lifestyle recommendations for all populations.

The biologic mechanisms whereby healthy lifestyles influence breast cancer risk are being extensively investigated (8) and include numerous pathways that are briefly mentioned by Arthur and colleagues (2). Future research, likely in the form of randomized controlled trials, will be needed to examine these combinations of risk factors simultaneously. To date, randomized clinical trials of lifestyle factors have been limited to one or two factors that are modified (e.g., dietary intake or physical activity) as studies that modify numerous factors simultaneously have not been considered feasible. However, with the advent of new technologies for tracking lifestyle factors (e.g., applications in smart phones), intervention trials of multiple risk factors may be considered possible in the future.

For now, there is a clear need to replicate these findings in other large-scale cohort studies that have jointly assessed lifestyle factors, preferably with objective measurements that are reliable, reproducible, and valid; some limitations existed with the WHI measurements as some were self-reported (e.g., physical activity was restricted to recreational activity only). The lack of effect of the diet score on breast cancer risk in the Arthur and colleagues' article (2) suggests that the HLI score should be modified to be more specific to breast cancer risk.

Considerable efforts are ongoing in numerous countries worldwide to quantify the current and future burden of cancer that can be attributable to modifiable risk factors for cancer (9, 10). These population-attributable risk estimates have traditionally been based on single risk factor estimates, whereas joint estimates of combined risk factors for cancer are needed to provide a more accurate estimate of how changing several factors simultaneously will influence cancer incidence.

Although the information from this study provides useful scientific data, it provides no new answers specifically on what women can do to reduce their risk for breast cancer, nor does it tell us whether reduction in one risk factor can overcome effects of another risk factor. For example, if a woman indulges in several glasses of wine on a Saturday night, can she counteract the adverse effects of alcohol on breast cancer risk by jogging a few miles on Sunday morning?

The study also does not give much information about the colinearity of the examined risk factors. For example, women who are physically active tend not to smoke and are likely to have a healthier diet than do sedentary women. Will these women benefit from the incremental change in HLI? Or, would most of the benefit occur in women who score most poorly in the index?

Ultimately, this research leads to primary prevention strategies that intervene on multiple risk factors simultaneously to reduce breast cancer risk. Evidence available to date demonstrates clear benefits on reducing exposures to alcohol, smoking, obesity, and increasing physical activity and improving dietary intake for reducing breast cancer risk. Knowledge remains limited, however, on how intervening on groups of risk factors concurrently will decrease breast cancer risk and what the possible future benefit will be in numbers of excess cancer cases that are avoided. Hence, future research efforts focused on examining joint risk factors for cancer risk are encouraged particularly from large-scale, prospective cohort studies with detailed and objective measures of these exposures. These analyses need to consider population subgroups defined by demographic characteristics, family history of cancer, clinical/pathologic tumor characteristics, and other possibly other molecular and genetic markers.

In the meantime, public health lifestyle recommendations remain unchanged for breast cancer risk reduction: minimize alcohol intake, exercise regularly, keep body mass index in the normal range, eat a healthy diet to prevent weight gain, and refrain from tobacco use (1).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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