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Physical activity and breast cancer: Quantitative risk assessment and investigation of insulin-like growth factor proteins as a potential molecular pathway

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Investigators have studied physical activity as a risk factor for breast cancer among women for over two decades. Seminal studies identified an inverse association between breast cancer risk and past participation in college sports. More recent epidemiological studies using detailed questionnaires have led to international recognition of physical inactivity as a probable risk factor for postmenopausal breast cancer. After extensive literature review, the Physical Activity Guidelines Advisory Committee, commissioned by the U.S. government, recommended in 2008 that women achieve up to an hour of moderate to strenuous activity every day in order to reduce breast cancer risk.

Despite broad recognition of physical activity's ability to modify breast cancer risk, uncertainty remains regarding its population- and molecular-level impacts. Determining physical activity's effect on population-wide breast cancer incidence can inform public health policymaking and help optimize resource allocation. Understanding physical activity's effects on molecular physiology can both help identify optimal forms of activity for breast cancer risk reduction and help elucidate biological mechanisms of breast cancer etiology. To address these research areas, two investigations were conducted for this thesis. The first was a quantitative risk assessment (QRA) calculating the proportion of postmenopausal invasive breast cancer in Germany that could be avoided through increases in physical activity under different scenarios. The second was a molecular epidemiology investigation among healthy women into the associations between physical activity and circulating peptide concentrations of IGF-I and IGFBP-3, two proteins implicated in breast cancer risk.

The proportion of disease incidence in a population that could be avoided by eliminating exposure to one or more risk factors is known as the population attributable risk (PAR). Calculating the PAR requires two inputs: the risk factor - disease relationship and the estimated risk factor distribution in the population of interest. This information can be gained from a case-control study, using the multivariable-adjusted odds ratios (ORs) from a logistic regression model and the risk factor distribution among case subjects. The present QRA employed data from the MARIE study, a large population-based case-control study conducted recently in two regions in Germany. A total of 3074 cases of postmenopausal invasive breast cancer and 6386 controls were included in this QRA. PARs for leisure-time activity (walking, cycling, and sports), non-leisure-time activity (occupational and household activities), and total physical activity since age 50 years were calculated. In addition to PARs regarding overall postmenopausal invasive breast cancer, PARs regarding breast cancer subtypes according to the estrogen receptor (ER) and progesterone receptor (PR) status of the tumor cells were calculated. A bootstrap method was used to estimate 95% CIs for the PARs. These methods were implemented using novel functions written for the statistical computing environment R.

The quantitative risk assessment resulted in a PAR for leisure-time physical activity of 12.8% (95%CI: 4.2% to 21.2%) regarding overall postmenopausal invasive breast cancer. This indicates that 12.8% of postmenopausal invasive breast cancer in Germany could be prevented if all women achieved at least 76.5 MET*hours/week of leisure-time physical activity from age 50 years onward. This level of activity is equivalent to one hour of cycling plus one hour of walking during leisure time per day.

Considering leisure-time physical activity and tumor subtypes according to ER/PR status, only the PAR regarding ER+/PR+ tumors (16.6% [95%CI: 7.5% to 25.8%]) was statistically significant. The PAR for total physical activity regarding ER+/PR- tumors (22.1% [95%CI: 5.2% to 39.5%]) was also statistically significant. These results could be an indication that physical activity modifies postmenopausal invasive breast cancer risk through pathways involving the estrogen receptor.

Members of the IGF protein family have been hypothesized to mediate the protective effect of physical activity on breast cancer risk. However, there is little evidence to support these hypotheses. To investigate the associations between physical activity and circulating IGF-I and IGFBP-3 concentrations, plasma samples from 426 pre- and 456 postmenopausal control subjects were selected from the GESBC and MARIE studies, respectively. The GESBC study, a population-based case-control study conducted in two areas in Baden-Württemberg, Germany, investigated breast cancer risk in women up to age 50 years. The MARIE study is described above. IGF-I and IGFBP-3 protein levels were measured using enzyme-linked immunosorbent assay kits. Log-linear regression techniques were used to determine associations between protein levels and leisure-time, non-leisure-time, and total physical activity as well as to test statistical interaction of these associations with menopausal status.

Among postmenopausal women, leisure-time physical activity was positively associated with IGF-I levels. Women in the lowest leisure-time activity category had 11% (95%CI: 3% to 19%) lower levels of circulating IGF-I than women in the highest category. There was some suggestion that postmenopausal women in the second highest total physical activity category had higher levels of IGFBP-3 than women in the highest category. In the association between leisure-time physical activity and IGF-I levels, the test of statistical interaction by menopausal status was significant, suggesting that this association differs by menopausal status. If circulating IGF-I or IGFBP-3 levels were to mediate the effects of physical activity on breast cancer risk, one would expect to observe inverse relationships between these proteins and activity levels. The observed positive association regarding IGF-I and lack of association regarding IGFBP-3 therefore suggest that neither protein plays a large role in the molecular pathway linking physical activity to breast cancer risk reduction.

This thesis details the first QRA of physical activity and breast cancer in Germany and is the first comprehensive QRA to address breast cancer subtypes according to ER/PR status. Furthermore, this is the first investigation of statistical differences in associations between physical activity and IGF proteins according to menopausal status. The results of the QRA indicate that over 12% of postmenopausal invasive breast cancer in Germany could be avoided through increases in leisure-time activities. This reduction was primarily attributable to ER+/PR+ breast tumors, which likely make up the majority of postmenopausal breast tumors in Germany. It is unlikely that circulating peptide concentrations of either IGF-I or IGFBP-3 mediate the reduced breast cancer risk due to increases in physical activity. However, high levels of IGF-I have been shown to be associated with better outcomes regarding other health conditions associated with aging. Therefore, encouraging women in Germany to achieve a high level of leisure-time activities could be expected to yield health benefits, including substantial reductions in the proportion of postmenopausal invasive breast cancer, the cancer with the highest incidence in Germany.