

# Determinants of breast cancer risk : focusing on mammographic density

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## Abstract

Breast cancer is the most common cancer and also one of the leading causes of cancer death among women worldwide. Since most known factors associated with breast cancer risk are difficult to influence, the potential of lifestyle factors, which are modifiable, in breast cancer prevention has recently been emphasised. Studies have shown a reduced risk of breast cancer among women who are more physically active, and an increased risk among women with higher alcohol consumption or cigarette smoking.

These lifestyle factors have been hypothesised to influence breast cancer risk through a mechanism that involves mammographic density, one of the strongest risk factors of the disease. Moreover, whether such associations might be modified by the women's background risk of breast cancer is unclear.

We therefore used data from the KARMA (KARolinska MAMmography) study to investigate the potential influence of background breast cancer risk on the association between physical activity (Study I,  $n = 38,913$ ), alcohol consumption (Study II,  $n = 53,060$ ), and cigarette smoking (Study III,  $n = 53,728$ ) and mammographic density. These lifestyle factors were assessed using self-administrated web-based questionnaires. Mammographic density was estimated using the fully-automated volumetric Volpara method and expressed as absolute dense volume, non-dense volume, and per cent dense volume. The Tyrer-Cuzick (TC) prediction model was used to estimate the individual background risk of developing breast cancer in the next 10 years.

In Study I, higher levels of physical activity were associated with a lower absolute dense breast volume and non-dense (adipose) breast volume, but a higher per cent dense breast volume among all women. After taking the TC 10-year risk of breast cancer into consideration, an association with lower absolute density was seen for all types of physical activity among women at low ( $< 3.0\%$ ) TC risk, for total and vigorous activities among women at moderate ( $3.0-4.9\%$ ) TC risk, and only for vigorous activity among women at high ( $\geq 5.0\%$ ) TC risk. In Study II, among all women we found an overall association between alcohol consumption and absolute and per cent dense breast volumes. Furthermore, alcohol consumption was only associated with a higher absolute dense volume among high-risk women. In Study III, current cigarette smoking was associated with lower absolute and per cent dense volumes, and this association was not found to be modified by TC 10-year background breast cancer risk. However, with respect to breast cancer risk, this finding should be viewed in light of the carcinogenic effects of cigarette smoking.

In the last study, we used prospective cohort data of 58,441 Swedish women of whom 522 developed invasive breast cancer. Overall, women with higher alcohol consumption had an increased risk of breast cancer compared to those with no alcohol consumption. After taking the TC background 10-year risk of breast cancer into account, alcohol consumption was only associated with breast cancer risk among women at moderate background risk.

## List of papers:

I. Background risk of breast cancer and the association between physical activity and mammographic density. Trinh T, Eriksson

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II. Background risk of breast cancer influences the association between alcohol consumption and mammographic density. Trinh T, Christensen SE, Brand JS, Cuzick J, Czene K, Sjolander A, Balter K, Hall P. British Journal of Cancer. 2015 Jun 30; 113(1):159-65.

[Fulltext \(DOI\)](#)



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III. Inverse association between cigarette smoking and mammographic density is independent of background breast cancer risk. Trinh T, Sjolander A, Cuzick J, Eriksson M, Balter K, Czene K, Hall P. [Submitted]

IV. Influence of background risk of breast cancer on the association between alcohol consumption and breast cancer risk. Trinh T, Sjolander A, Eriksson M, Cuzick J, Balter K, Czene K, Hall P. [Manuscript]

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has shown that women with dense breasts can be 6 times more likely to develop breast cancer. Learn more about breast density. This increases the risk that cancers will be missed. Women with dense breasts have a higher risk of developing breast cancer compared to women with mostly fatty breasts. The greater the amount of dense tissue, the higher the risk. However, you don't necessarily have a high risk of breast cancer just because you have dense breasts. Breast density has to be considered along with other risk factors, such as age, family history, and any personal history of breast changes that increase cancer risk. Mammographic density: Evidence based insights into the biology of breast tissue. We propose that cumulative exposure to mammographic density may be an important determinant of breast cancer incidence, and that the risk for breast cancer associated with mammographic density may be explained by the combined effects of mitogens, which influence cell proliferation and the size of the cell population in the breast, and mutagens, which influence the likelihood of genetic damage to those cells. Figure 1 panels a and b, respectively, provide a schematic overview and a more detailed description of aspects of these hypotheses that are examined in the sections that follow. The availa