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Initiators and promoters for the occurrence of screen-detected breast cancer and the progression to clinically-detected interval breast cancer

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ABSTRACT

Background: The risk factors responsible for breast cancer have been well documented, but the roles of risk factors as initiators, causing the occurrence of screen-detected breast cancer, or promoters, responsible for the progression of the screen-detected to the clinically-detected breast cancer, have been scarcely evaluated.

Methods: We used data from women in a cohort in Kopparberg (Dalarna), Sweden between 1977 and 2010. Conventional risk factors, breast density, and tumor-specific biomarkers are superimposed to the temporal course of the natural history of the disease.

Results: The results show that older age at first full-term pregnancy, dense breast, and a family history of breast cancer increased the risk of entering the preclinical screen-detectable phase of breast cancer by 23%, 41%, and 89%, respectively. Overweight/obesity (body mass index $\geq$25 kg/m^2) was a significant initiator (adjusted relative risk [aRR] 1.15; 95% confidence interval [CI], 0.99–1.33), but was inversely associated with the role of promoter (aRR 0.65; 95% CI, 0.51–0.82). Dense breast (aRR 1.46; 95% CI, 1.12–1.91), triple-negative (aRR 2.07; 95% CI, 1.37–3.15), and Ki-67 positivity (aRR 1.66; 95% CI, 1.19–2.30) were statistically significant promoters. When the molecular biomarkers were considered collectively as one classification, the basal-like subtype was the most influential subtype on promoters (aRR 4.24; 95% CI, 2.56–7.02) compared with the Luminal A subtype.

Discussion: We ascertained state-dependent covariates of initiators and promoters to classify the risk of the two-step progression of breast cancer. The results of the current study are useful for individually-tailored screening and personalized clinical surveillance of patients with breast cancer that was detected at an early stage.

1. Introduction

Hormonal risk factors that are responsible for breast cancer have been well documented since 1980.[1,2] The majority of studies place emphasis on whether or not breast cancer occurs. Mathematical models that predict the risk of breast cancer, such as the Gail model, have been proposed for such a purpose.[3–7] In the era of preventive medicine, a simple relationship of a particular risk factor to the occurrence of breast cancer is not sufficient. Considering the

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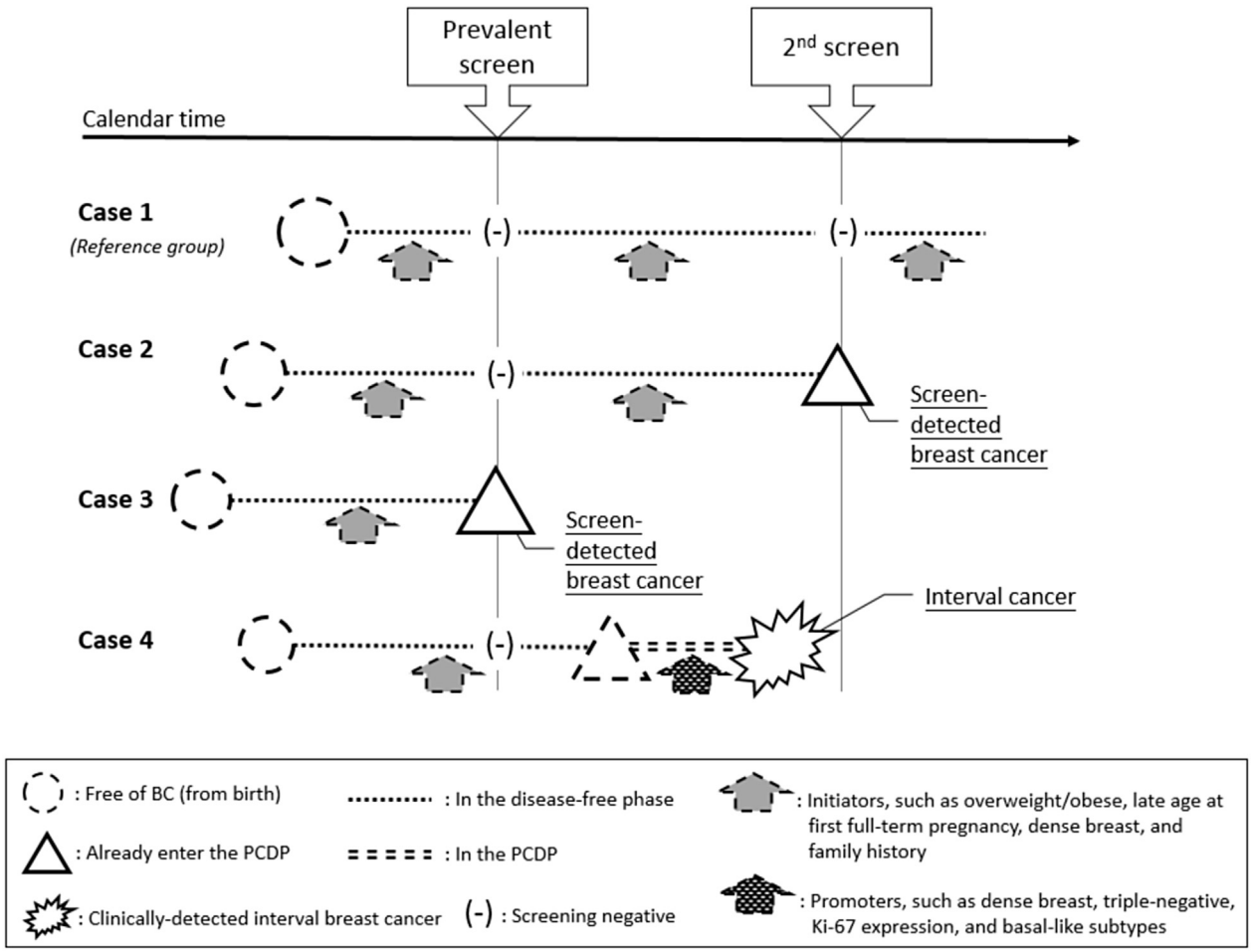

Fig. 1. Breast tumors that remained in the PCDP and the CP, as represented by screen-detected and clinically-detected interval breast cancers in relation to initiators and promoters. * The dashed line represents the unobserved status, while the solid line and underscored text represent the observed status. BC, breast cancer; CP, clinical phase; PCDP, pre-clinical detectable phase.

dynamic process of the development of breast cancer as shown in Fig. 1, women experience a pre-symptomatic phase before they progress to the symptomatic phase. The majority of women are initially free of breast cancer (case 1). In cases of breast cancer, the tumor develops as a very small and pre-symptomatic lesion, which is undetectable. As time passes, the tumors clone and grow to a detectable size, and although women may still be pre-symptomatic during this phase, the tumor can be detected using available screening tools, such as mammography; even at this stage, women may still not exhibit any symptoms and signs (the so-called pre-clinical detectable phase [PCDP]). The PCDP is the window of early detection. If the lesion is detected through screening during the period when women are in the PCDP, they are defined as "screen-detected cases" (case 2 and case 3). If women enter the PCDP after screening but progress to a clinical phase after they feel lumps or experience symptoms and signs (the clinical phase [CP]) and then seek medical care, these are defined as "interval cancers" (case 4). The risk factors of interest may be related to the rate of entering the PCDP (initiators) and also may be responsible for the subsequent progression from the PCDP to the CP (promoters). The elucidation of the function of each risk factor with respect to its role as an initiator or a promoter is of great importance to individually-tailored screening and personalized clinical surveillance.

However, the classification of each risk factor as an initiator or a promoter is a great challenge unless the data from a population-based breast cancer screening are considered. These data provide an opportunity to assess the relative contribution between initiators and promoters through a comparison of the distribution of each risk factor between screen-detected breast cancers (pre-symptomatic cases that remained in the PCDP) and clinically-detected breast cancers. An example of clinically-detected breast cancer is interval cancer, which represents progression of cancer from the PCDP that was already found at a previous screen and was missed or that progressed to the CP after the screen but before subsequent screening (i.e., symptomatic cases). In addition to the conventional hormonal risk factors, information on the status of estrogen receptor (ER), progesterone receptor (PR), HER-2/neu, and Ki-67, as well as the presence of a basal-like phenotype, are widely used to predict the prognosis of breast cancer; these additional factors are also very informative with respect to the rate of progression from the pre-symptomatic phase to the symptomatic phase.[8–10] Because only breast tumor cases have such information, it is postulated that if the distributions of these factors are different between screen-detected and clinically-detected interval cancers, these tumor-specific markers might play a crucial role as promoters.

In the current study, we aimed to use longitudinal follow-up data from Kopparberg (Dalarna) county in the Swedish two-county trial of mammography screening. We applied a four-state continuous-time Markov regression model to estimate the

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