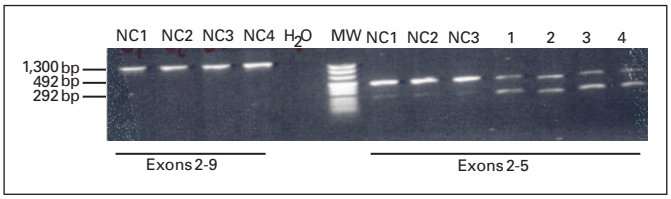

Fig 2. Comparative results of reverse transcriptase–polymerase chain reaction with primers 1FcDNA/10RcDNA (exons 2 to 9) and 1′FcDNA/5RcDNA (exons 2 to 5). Using primers 1FcDNA/10RcDNA the c.156_157insAlu-negative controls (NC) show only the expected product (approximately 300 bp) is observed in positive (1 to 4) and negative (NC1-NC3) samples.

been described in different tumor specimens[2,5-7] and have probably been erroneously associated with intronic variants.[7] Therefore, the intronic variants referred to by Díez et al may not be the cause of exon 3 skipping and most probably represent *BRCA2* polymorphisms without pathogenic relevance. Exon 3 skipping in a *BRCA2* alternative transcript results from a physiological splicing mechanism whose relevance for cellular function is still unknown. In contrast, the c.156_157insAlu-mediated exon 3 skipping occurs in the main 27-exon *BRCA2* transcript with the resulting BRCA2 protein lacking the two transactivation domains. This loss is predicted to cause the BRCA2 protein to be dysfunctional as in the case of the other rearrangement that also mediates exon 3 skipping in the main *BRCA2* transcript.[3]

Although c.156_157insAlu is still the most frequent *BRCA2* rearrangement described due to its founder effect in the Portuguese population, the identification of more *BRCA2* rearrangements[8-10] is clearly important, since it will definitely contribute to the genetic screening of breast cancer risk families without identified cancer predisposition mutations.

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Does the Decrease in Hormone Replacement Therapy Also Affect Breast Cancer Risk in the Netherlands?

To the Editor: Recently, Robbins and Clarke[1] reported a sharp decrease in the incidence rate of first primary breast cancer in women throughout 50 years in the United States, which was attributed to a decrease in hormone replacement therapy (HRT) since 2001, consistent to an earlier study that was also done in the United States.[2] Although there was a similar decrease in HRT across Europe, such a remarkable decline in breast cancer rates has only been reported in Germany.[3] Generally, women in Europe have shown a different pattern of HRT use than the United States, mostly less frequent use and of shorter durations.[4,5] Only 13% of women aged 49 to 70 years used HRT in the Netherlands between 1993 and 1997,[5] versus 38% in the United States.[4] In the Netherlands, HRT use decreased by 12% between 2002 and 2003, followed by another 26% between 2003 and 2004. By the end of 2005, there was a decrease of 42%, as compared to 2001, of combined estrogen-progesterone and natural and semiorganic estrogen use. However, the rate of first primary breast cancer among women aged 50 to 69 years in the northwestern and southeastern Netherlands had not changed until 2005 (Fig 1). The impact of the sudden fall of HRT use would account for about a 6% fall of breast cancer incidence in the United States versus only 0.4% in the Netherlands, using the following formula $(p\text{-}p^*)(\text{relative risk [RR]} - 1) / (p\,[RR - 1] + 1)$[6] ($p$ = past prevalence, p^* = current prevalence and RR is 1.07 for the Netherlands for duration of use < 5 years and 1.25 for the United States for duration of use ≥ 5 years[7]). A similar small impact of decrease in HRT use on the breast cancer incidence is expected in low-use countries such as Spain or Italy (5% to 8%), which is in contrast to countries with a high use such as Belgium or France (32% to 38%).[4] There is, however, another pitfall; HRT use has been related to increased breast density, thus reducing the specificity of mammography and delaying detection of 20% of breast cancer cases.[8] The maximum benefit of HRT reduction should be evident within the

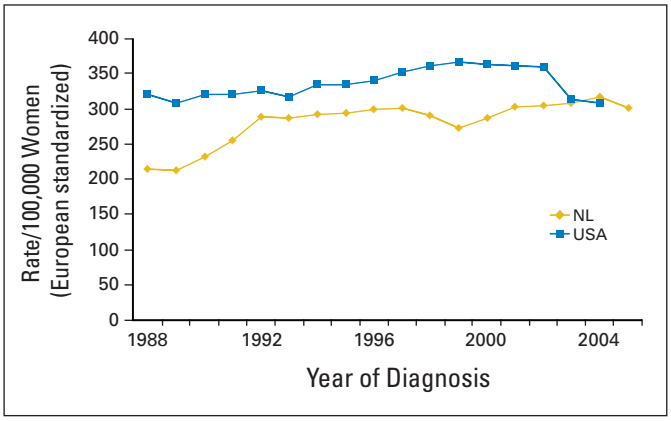

Fig 1. Annual incidence of female breast cancer between the ages of 50 and 69 years in the Netherlands (NL) and in the United States (USA). US data are from nine of the Surveillance Epidemiology and End Results registries, and NL data are from two registries (northwest and southeast NL). Data of the NL for 2004 to 2005 (northwest) and 2003 to 2005 (southeast) are corrected for extra regional cases by adding the average number of extra regional cases in preceding years. Rates were age adjusted to the European standard population.

next 2 years (data until 2007) in the Netherlands, where biannual mass screening with more than 80% attendance rate has been practiced since the early 1990s, and might take longer in the United States having only opportunistic screening with lower coverage and attendance rate.

The two cancer registries involved have proven to be a valuable source of data.[9] Currently, only a flattening of the 40-year rising trend in breast cancer incidence following the decrease of HRT use has been observed, warranting more years of observation.

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In Reply: Soerjomataram and colleagues point out the wide range in prevalence of hormone therapy (HT) use across Europe during the 1990s, from the Netherlands, where HT use was one-third that in the US, to Germany,[1] where it was comparable to the United States. They also nicely summarize the mathematical considerations underlying HT-related changes in breast cancer incidence. They correctly point out that only small decreases in breast cancer incidence would be expected after HT declines if (1) the absolute prevalence of HT use was low to begin with; or (2) most of the HT use was short term. In the Netherlands, both of these conditions applied; in California, neither did. Furthermore, HT-associated relative risks may depend on formulation; in North America, women more commonly use conjugated equine estrogen and medroxyprogesterone acetate, while in Europe, common HT preparations include estradiol and other progestins (eg, micronized progesterone).

Thus, the absence of a perceptible drop in breast cancer in the Netherlands after 2001 is not surprising and is entirely consistent with our data from California,[2] and with other recent data documenting strong correlations between population-level HT use and breast cancer incidence in well-screened populations in the United States.[3,4] Besides the report from Germany,[1] other reports have recently been published describing breast cancer incidence trends in Geneva, Switzerland,[5] Canada,[6] Norway,[7] Sweden,[8] and New Zealand.[9] In interpreting these data, we concur with our Dutch colleagues that large declines in the incidence of breast cancer are not always expected after substantial declines in the prevalence of HT use. We also second their call for continued close monitoring of international data in coming years, which will help us to more fully understand the HT/breast cancer relationship, in light of the worldwide "natural experiment" that occurred after the early termination of the estrogen/progestin arm of the Women's Health Initiative.

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