

## Response

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We thank Dr. Lawson for his comments and for the opportunity to further discuss our hypothesis that breast cancer comprises a mixture of two main etiological subtypes. Though Weigelt and Reis-Filho considered our two-component mixture model “contentious,” they nonetheless noted that the etiological concepts were consistent with the molecular evidence (1).

Notwithstanding Dr. Lawson's suggestion of a viral cause for breast cancer, current evidence for an important etiological role for viruses in breast cancer is reported to be minimal, as reviewed by Joshi and Buehring (2). Tang et al. also did not find any evidence for a viral origin in breast cancer, based upon transcriptomic sequencing for known and novel viruses in 810 breast tumors from the Cancer Genome Atlas Research Network (3). Furthermore, traditional breast cancer risk factors do not suggest a communicable etiology, in contrast with most viral infections, notably with papillomaviruses (4).

We agree with Drs. Caldarella and Crocetti that it would be useful to further explore the age distribution of breast cancer in different countries and over time to determine if bimodality is a universal characteristic of female breast cancer. Of note, bimodal female breast cancer was first observed as early as 1930 in Germany, and subsequently reported in Africa, Asia, Italy, and Europe, in addition to America (5). Drs. Caldarella and Crocetti show a unimodal density plot for estrogen receptor (ER)-negative breast cancers from their Tuscan Cancer Registry. However, as we have acknowledged, mixtures can generate a broad spectrum of density curves, and multimodal peaks can be difficult to discern if the peaks are close together or if sample size is small, as in their Tuscan dataset (6). Additionally, though unimodal (ie, one predominant peak frequency), their density plot shows heavy tails, suggesting that a mixture model would provide a better fit to their data than a single density.

Two recent publications provide additional support for our two-component mixture conceptual framework (7,8). In an integrative molecular analysis of 12 cancer types within the Cancer Genome Atlas Research Network, Hoadley et al. demonstrated a unique pattern for two main breast cancer groups, which distinguished basal-like cancers from the luminal and HER2-enriched intrinsic subtypes (7). Palmer et al. present further evidence

for two different risk factor patterns between ER-positive and ER-negative cancers (8). Palmer et al. show that parous women have a reduced risk of ER-positive tumors but an increased risk of ER-negative cancers, especially triple-negative tumors (a correlate of basal-like cancers), and that this risk can be attenuated with breastfeeding.

In sum, emerging molecular (7) and epidemiological (8) evidence provides additional support for a parsimonious view of breast cancer etiology due to varying proportions or mixtures of two main etiological subtypes. Epidemiologists have largely used ER-positive and ER-negative cancers as useful proxies for the two breast cancer subtypes. Luminal and basal-like intrinsic cancers now appear to be even more associated with the two putative etiological subtypes. In fact, rather than being considered as two different subtypes of breast cancer, luminal and basal-like tumors might be better thought of as two completely different cancers that occur in the breast.

## References

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