Mammary Involution and Breast Cancer Risk: Transgenic Models and Clinical Studies

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Abstract Postlactational involution is the process following weaning during which the mammary gland undergoes massive cell death and tissue remodeling as it returns to the pre-pregnant state. Lobular involution is the process by which the breast epithelial tissue is gradually lost with aging of the mammary gland. While postlactational involution and lobular involution are distinct processes, recent studies have indicated that both are related to breast cancer development. Experiments using a variety of rodent models, as well as observations in human populations, suggest that deregulation of postlactational involution may act to facilitate tumor formation. By contrast, new human studies show that completion of lobular involution protects against subsequent breast cancer incidence.

Keywords Postlactational involution · Lobular involution · Transgenic models · Clinical studies · Breast cancer risk

Abbreviations

ATF4	activating transcription factor 4
C/EBPδ	CCAAT/Enhancer Binding Protein δ
Cox-2	cyclooxygenase-2
CSF-1	colony stimulating factor-1
ECM	extracellular matrix
EGFR	epidermal growth factor receptor
FGF4	fibroblast growth factor 4
IGF	insulin-like growth factor
IKK2	IκB kinase 2/β
IL-6	interleukin-6
IL-10	interleukin-10
IRF-1	interferon regulatory factor-1
LAR	leukocyte antigen related
LIF	leukemia inhibitory factor
Mfge8	Milk fat globule-EGF-factor 8
MMP-3	matrix metalloproteinase-3
TA1	metastasis-associated protein 1
MUC1	mucin
Plg	plasminogen
RANK	receptor activator of nuclear factor-κB
SOCS3	suppressor of cytokine signaling 3
STAT3	signal transducer and activator of transcription 3
STAT5a	signal transducer and activator of transcription 5a
TBRII	transforming growth factor β receptor II
TGFα	transforming growth factor alpha
TGFβ	transforming growth factor β
VDR	vitamin D_3 receptor

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Introduction

Cancer can be viewed as a disease of defective development, wherein the signaling processes that guide normal tissue growth and morphogenesis become deregulated to facilitate cancer cell proliferation and tissue invasion. For breast cancer specifically, a large body of research has focused on the role of developmental signaling pathways in tumor progression; progress in this area has been facilitated in part because unlike most organs, the majority of mammary development occurs postnatally. At birth, the

mammary gland is present as a primitive anlage; during puberty, the epithelium branches and grows to fill the gland. Importantly, many of the cellular processes that control branching morphogenesis during normal breast development are found to participate in tumor growth and invasion as well [1].

Breast development does not stop with puberty; the mature mammary gland also undergoes dramatic changes with each cycle of pregnancy/lactation/postlactational involution (Fig. 1). During early pregnancy, the epithelium proliferates extensively to form tissue structures for producing milk, and then during late pregnancy and lactation the epithelial cells differentiate further to become specialized for high levels of milk component production. After lactation is complete, weaning of the infant induces postlactational involution, a process in which the majority of epithelial cells rapidly undergo programmed cell death and the remaining cells are remodeled into a glandular structure that resembles the prepregnant state. As postlactational involution represents an important mechanism for removing unnecessary epithelial cells in a regulated fashion, in many ways this process appears diametrically opposed to the uncontrolled epithelial proliferation evident in cancer. Accordingly, there has been much interest in defining how the signaling processes present in postlactational involution become deregulated in cancer, where intrinsic cell apoptosis mechanisms become suppressed. Investigations using animal models have revealed many of the specific mediators of involution-associated apoptosis, remodeling, and inflamma-tion, and also how selective modulation of these mediators affect both the process of postlactational involution and propensity for cancer development [2].

With organismal aging, there is a loss of breast epithelial tissue which is distinct from postlactational involution, in which the mammary gland gradually loses complexity and function. In humans, this phenomenon has been defined as age-related lobular involution. Lobular involution begins in perimenopause and accelerates during menopause, and is characterized as a decrease in the size and complexity of the ductal tree and of the terminal ductal lobular units (TDLU) [3]. While much remains to be learned about how lobular involution is regulated, recent clinical studies have shown that the process of lobular involution has considerable significance for development of breast cancer, as premenopausal women who were found to have undergone partial or complete lobular involution were also found to have substantially decreased risk of breast cancer, while postmenopausal women who showed delayed lobular involution were found to have a correspondingly elevated breast cancer risk [4]. These findings suggest that reduction of epithelial tissue associated with lobular involution may be a physiologically protective mechanism against breast cancer. In this review, we will briefly describe the processes of postlactational involution and lobular involution, and highlight investigations of these processes that have provided insight into mechanisms of cancer development and suggested new approaches for prevention or treatment of breast cancer.
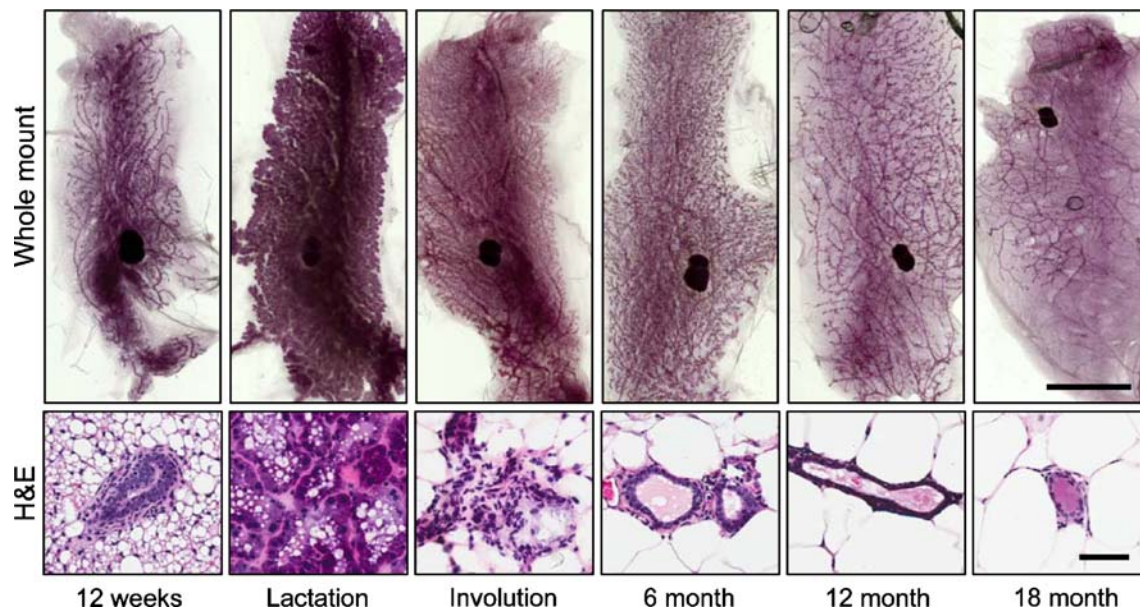

Figure 1 Mouse mammary gland morphogenesis. Whole mounts (top row) and hematoxylin and eosin (H&E, bottom row) images of fourth inguinal mammary glands. 12-week old mice have developed a ductal tree that fills the fat pad. Lactating mice show extensive glandular growth and cellular differentiation, and this phenotype is rapidly lost during postlactational involution. Aging mice show gradual degeneration of the mammary gland so that by 18 months, only a spindly ductal structure remains. Scale bar for whole mount, 1 cm; for H&E, 50 μm.

Postlactational Involution and Breast Cancer

Mice provide a useful, tractable model for studying postlactational involution, as normalization of the number of suckling pups standardizes mammary differentiation during lactation, and simultaneous removal of suckling pups induces postlactational involution in a synchronous fashion. Studies employing mouse models have shown that postlactational involution proceeds through an initial, reversible stage in which there is widespread apoptotic cell death, followed by an irreversible second stage in which the mammary gland is remodeled to the pre-pregnant state [5]. The first stage is triggered by cessation of suckling, whereupon continued milk production causes distension of the alveolar lumen. Nipple sealing experiments have shown that this milk stasis is sufficient to induce the first stage of postlactational involution, in which epithelial cells are shed into the acinar lumen [6, 7]. These shed cells express markers of apoptosis, including redistribution of phosphatidylserine to the outer leaflet of the cell membrane and cleavage of the key apoptosis mediator caspase 3 [8], although it is not clear whether apoptosis in these cells is a cause or consequence of detachment from the basement membrane [5].

The second, irreversible stage of postlactational involution begins at approximately 48 h after weaning. A gradual reduction of circulating hormones during the first stage is necessary for progression to this stage [7, 9]. Here, there is glandular collapse, redifferentiation of adipocytes, and remodeling of the ductal epithelium. Breakdown of the basement membrane, a specialized extracellular matrix that surrounds the mammary epithelium, is a key step in tissue remodeling, and there is substantial expression of serine and matrix metalloproteinases during the second stage of involution [10]. Associated with loss of the basement membrane, caspase 3-staining can be seen in the acinar cell wall by 72 h.

While postlactational involution is normally a highly controlled process, the rapid and extensive tissue breakdown and remodeling is not without risk. The highly reactive nature of the remodeling gland is reminiscent of pathological conditions such as wound healing and tumor development. The proteinase expression profiles in the remodeling gland are similar to that found in developing breast tumors [11], and transcriptional profiling studies have provided evidence of the activation of many inflammatory processes, including both innate and adaptive immune responses [12–14]. These studies found an increase in proinflammatory cytokines and neutrophil chemoattractants during the first stage of involution, followed by a more sustained elevation of chemoattractants for and markers of monocytes and macrophages during the second stage. There were also a substantial number of transcripts for immunoglobulins, indicating the presence of activated B-cells. Analysis of the transcriptional profiles of post-lactatational glands revealed a high level of similarity to those found in wound healing and the tumor microenvironment, including expression of many growth factors, cytokines, and tissue morphogens [15, 16].

Although postlactational involution normally proceeds without pathological consequences, the deregulation of tissue structure and activation of tumor microenvironment characteristics may act to facilitate the outgrowth of premalignant cells present in the mammary gland [17]. This possibility has been validated by experiments which isolated extracellular matrix (ECM) from nulliparous or postlactational mammary glands, and found that ECM from the remodeling glands contained tumorigenic ECM fragments that could facilitate outgrowth of breast cancer cells in culture, as well as promote increased breast cancer metastasis in animal models [18–20]. Intriguingly, the tumor-promoting potential of the involuting mammary gland has been suggested to underlie the elevated incidence of breast cancer associated with pregnancy [17].

Transgenic Models of Postlactational Involution

A number of gene promoters are active in mammary epithelial cells, and some are specifically activated during pregnancy. Transgenic mouse models that use these promoters to selectively activate or remove a particular gene from mammary epithelial cells have greatly facilitated the dissection of mammary gland developmental processes. To date, more than 50 transgenic mouse models have been reported to show alterations in postlactational involution (Table 1). In many cases, the effect on involution is consistent with previously identified expression patterns in the involuting gland. Postlactational involution is inhibited by the deletion of cytokines normally upregulated in the involuting gland, such as FasL [21], IL-6 [22], IL-10 [23], and LIF [24], and is accelerated by their premature expression, as for TGF-β3 [25]. Similarly, manipulation of cell death pathways also alters the timing of postlactational involution: deletion of the apoptosis inducer Bax delays involution, while decreased expression of the apoptosis inhibitor Bcl2 accelerates involution [26, 27]. The secreted protein milk fat globule-EGF-factor 8 (Mfge8) binds to apoptotic cells through recognition of phosphatidyl serine in the outer leaflet and has been implicated in phagocytosis; mice lacking Mfge8 have decreased clearance of apoptotic cells and delays in the second stage of postlactational involution [28, 29].

Transgenic models also have provided insight into the complexity of the processes that govern postlactational involution. Mammary gland remodeling is associated with

Table 1 Transgenic mice with involution phenotypes and effects on tumor formationc.

Transgenic model	Involution effect	Mammary tumor effect
Akt2 deletion	Delayed [61]	Promoted [62]
MMTV-Akt1	Delayed [39, 41, 42]	Promoted [39, 40]
Bax deletion	Delayed [27]	Promoted [43]
WAP-Bcl-2	Delayed [26, 27]	Promoted [26, 44]
Bin1 deletion	Delayed [63]	Promoted [63]
MMTV-p130Cas	Delayed [64]	Promoted [64]
MMTV-ΔN89β-Catenin	Delayed [65]	Spontaneous [65]
MMTV-Cdc25B	Delayed [66]	Promoted [67]
C/EBPδ deletion	Delayed [68]	Promoted[a]
MMTV-Cox-2	Delayed [69]	Spontaneous [69]
MMTV-CSF-1	Delayed [70]	Spontaneous [70]
MMTV-EGFR	Delayed [71]	Spontaneous [71, 72]
MMTV-EphB4	Delayed [73]	Promoted [73]
MMTV-ErbB2/neu	Delayed [38]	Spontaneous [37]
WAP-FGF4	Delayed [74]	Unknown
FasL deletion	Delayed [21]	Unknown
MMTV-c-fms	Delayed [70]	Spontaneous [70]
gp130 deletion	Delayed [75]	Unknown
WAP-IGF1	Delayed [76–78]	Promoted [79]
MMTV-IGF2	Delayed [80]	Spontaneous [81]
IKK2 deletion	Delayed [82]	Unknown
IL-6 deletion	Delayed [22]	Unknown
IL-10 deletion	Delayed [23]	Unknown
Jak2 deletion	Delayed [80, 83]	Unknown
LIF deletion	Delayed [24]	Unknown
Mfge8 deletion	Delayed [28, 29]	Unknown
MMTV-MTA1	Delayed [84]	Spontaneous [84]
MMTV-MUC1	Delayed [85]	Spontaneous [85]
Mnt deletion	Delayed [86]	Spontaneous [87]
MMTV-Notch1	Delayed [88, 89]	Spontaneous [88, 89]
p53 depletion (BALB/c)	Delayed [90]	Spontaneous [91]
Plg depletion	Delayed [34]	Unknown
PTEN deletion	Delayed [92]	Spontaneous [92]
MMTV-RANK	Delayed [93]	Promoted[b]
STAT3 deletion	Delayed [94, 95]	Unknown
TBRII deletion/inhibition	Delayed [96, 97]	Enhanced [97–99]
WAP-TGFα	Delayed [100]	Spontaneous [100]
VDR deletion	Delayed [101]	Spontaneous [102, 103]
Akt1 deletion	Premature [61]	Inhibited [62]
Lactoglobulin-ATF4	Premature [104]	Unknown
β1-integrin inhibition/deletion	Premature [105]	Inhibited [106]
Bcl-x deletion	Premature [107]	Unknown
MMTV-Cripto-1	Premature [46]	Spontaneous [46, 47]
IRF deletion	Premature [108]	Unknown
LAR deletion	Premature [109]	Unknown
WAP-MMP-3	Premature [32, 33, 35]	Spontaneous [48, 49]
MMTV-myc	Premature [26]	Spontaneous [50]
SOCS3 deletion	Premature [110]	Unknown
STAT5a deletion	Premature [111]	Inhibited [111, 112]

Table 1 (continued).

Transgenic model	Involution effect	Mammary tumor effect
TIMP3 deletion	Premature [113]	Unknown
Lactoglobulin-TGFβ3	Premature [25]	Unknown

ATF4 activating transcription factor 4; *C/EBPδ* CCAAT/Enhancer Binding Protein δ; *Cox-2* cyclooxygenase-2; *CSF-1* colony stimulating factor-1; *EGFR* epidermal growth factor receptor; *FGF4* fibroblast growth factor 4; *IGF* insulin-like growth factor; *IKK2* IκB kinase 2/β; *IL-6* interleukin-6; *IL-10* interleukin-10; *IRF-1* interferon regulatory factor-1; *LAR* leukocyte antigen related; *LIF* leukemia inhibitory factor; *Mfge8* Milk fat globule-EGF-factor 8; *MMP-3* matrix metalloproteinase-3; *TA1* metastasis-associated protein 1; *MUC1* mucin; *Plg* plasminogen; *RANK* receptor activator of nuclear factor-κB; *SOCS3* suppressor of cytokine signaling 3; *STAT3* signal transducer and activator of transcription 3; *STAT5a* signal transducer and activator of transcription 5a; *TBRII* transforming growth factor β receptor II; *TGFα* transforming growth factor alpha; *TGFβ* transforming growth factor β; *VDR* vitamin D$_3$ receptor

[a] personal communication, Esta Sterneck

[b] personal communication, William McDougall

increased expression of a number of proteases, including matrix metalloproteinase-3 (MMP-3) and plasminogen (Plg) [30, 31]. Accordingly, induced expression of MMP-3 causes premature involution while deletion of Plg causes delays in glandular remodeling [32–35]. However, further examination reveals that these proteases affect mammary gland development though multiple mechanisms. Mice lacking MMP-3 do not show a significant delay in involution but rather altered differentiation of adipocytes [33], potentially implicating overlapping functions of different MMPs; mice lacking Plg show evidence of premature activation of the first stage of postlactational involution, possibly through increased milk production in these mice [36].

Many of these transgenic mouse models revealed unexpected connections between the processes of postlactational involution and mammary tumor growth and progression. In some cases, mouse models which were created to investigate the effects of increased expression of breast oncogenes (ErbB2/neu [37, 38] and Akt1 [39–42]) were found subsequently to have delays in postlactational involution. Similarly, many of the transgenic mice that show alterations in postlactatational involution also show increased tumor development or progression. In some of these cases, the connection between the two phenomena is straightforward: suppression of cell death delays involution and facilitates tumor progression in mice lacking Bax [27, 43] or expressing Bcl-2 [26, 27, 44] or Akt1 [39, 41, 42].

For many transgenic mice showing both delayed postlactational involution and increased tumor production, the relationship between the two functions is not clear. In some cases, there may be unexpected, yet-to-be-identified tumor signaling pathways. However, another possibility is that delayed involution enhances the intrinsic tumor promoting capability of the postlactational mammary gland, identified in cell culture and animal studies and implied by the increased incidence of pregnancy-associated breast cancer in humans [17]. Moreover, as disruption of tissue structure can activate genomic instability [45], prolonged postlactational involution could potentially foster both cancer initiation and progression.

Examples that appear at variance with the correlation between delayed postlactational involution and increased tumorigenesis include mice overexpressing Cripto [46, 47], MMP3 [32, 33, 35, 48, 49] or myc [26, 50], which show premature involution but increased incidence of cancer. In some cases, the transgene may impair mammary development during pregnancy, which could complicate comparisons of involution rates, as has been suggested for mice overexpressing Cripto [46, 47]. While the reason for premature involution in MMP3-and myc-overexpressing mice remains unclear, these models may reflect activation of common signaling pathways, as exposure of mammary epithelial cells to MMP3 was previously found to increase expression of myc [51]. We point out that for many of the transgenic mice with defects in postlactational involution, the effect on tumor progression remains unknown; similarly, many mammary tumor models have never been investigated for rate of postlactational involution, and this represents a critical area for future research. More complete characterization of the involution phenotype for mammary tumor-associated transgenic mouse models may eventually assist in unraveling the complex relationships between involution pathways and cancer.

Lobular Involution and Breast Cancer

Lobular involution is a distinct process from postlactational involution. Unlike the dramatic cell death and morphogenesis following weaning, lobular involution is associated with a gradual decrease in the complexity and extent of ductal epithelium with age (Fig. 2). While aging mice show an epithelial degeneration process that is reminiscent of lobular involution (Fig. 1), most research about lobular involution has focused on human studies. While there are
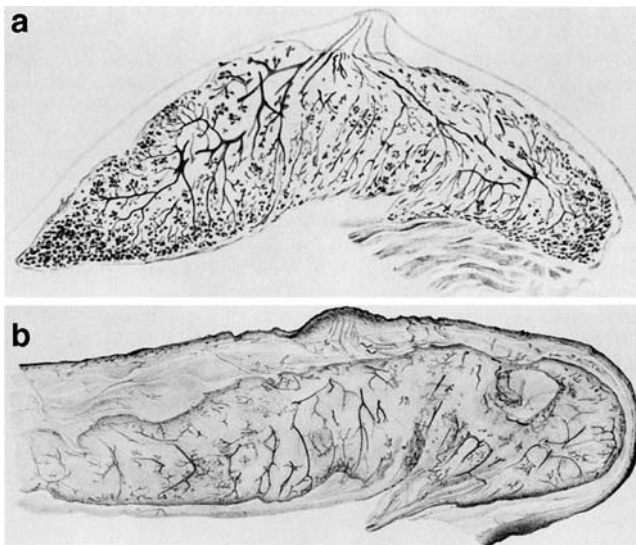
Figure 2 Breast whole mounts of preinvolutional (**a**) and postinvolutional (**b**) women. Reprinted with permission of Springer Science+ Business Media. Originally published in "Handbuch der mikroskopischen Anatomie des Menschen." (W. Bargmann, ed.), Vol 3, part 3, Haut und Sinnesorgane, pp. 277–485, 1957. Springer-Verlag, Berlin).

substantial similarities between human and mouse mammary glands, there are important differences as well. The human breast is organized into 15–20 major lobes, each made up of lobules that contain the milk-forming acini; the acini are grouped at the ends of the ducts to form structures known as terminal duct lobular units (TDLUs; see inset, Fig. 3a). During pregnancy and lactation, the TDLUs develop into secretory, milk-producing, lobular alveoli, and the surrounding fat cells diminish [52]; during postlactational involution, the TDLUs return to the pre-pregnant state without a cumulative loss of glandular tissue [53, 54]. By contrast, age-related lobular involution appears to be an irreversible process, in which the number and size of acini per lobule are reduced and the delicate intralobular stroma is replaced with collagen from connective tissue (Fig. 3b) [3]. Ultimately the glandular epithelium and stroma regress and are replaced by fat [55]. The tempo and extent of lobular involution vary considerably among individual women [3]; in an autopsy series, evidence that lobular involution had begun was found in up to 33% of women younger than 40 years of age [56].

A recent study investigated pathological characteristics of a large cohort of women who had breast biopsies with benign findings (benign breast disease, BBD) at the Mayo Clinic [57]. Besides evaluating the standard features such as extent of epithelial proliferation and the presence or absence of atypia in these samples, this study noted the extent of lobular involution that had occurred in the normal breast lobules, and found that lobular involution was associated with a significantly reduced risk of breast cancer [4]. While this finding is consistent with the widespread understanding that lobules (or

TDLUs) are the anatomic substructure that gives rise to breast cancer [58], this study was particularly significant in that progressive degrees of involution were associated with reduced cancer risk in high-risk subsets defined by age, atypia, reproductive history or family history (Fig. 4). For example, women over age 55 without demonstrable lobular involution had a 3-fold increased risk of breast cancer over same-aged women with complete involution (Fig. 4). Of note, about 5% of women before age 50 had complete involution of their breast tissue, while complete involution was seen in more than 20% of women aged 50–59, presumably coinciding with menopause [4]. Interestingly, the step-up in completion of involution around age 50 coincides with the well-recognized slowing in the rate of increase of breast cancer at that age, raising the possibility
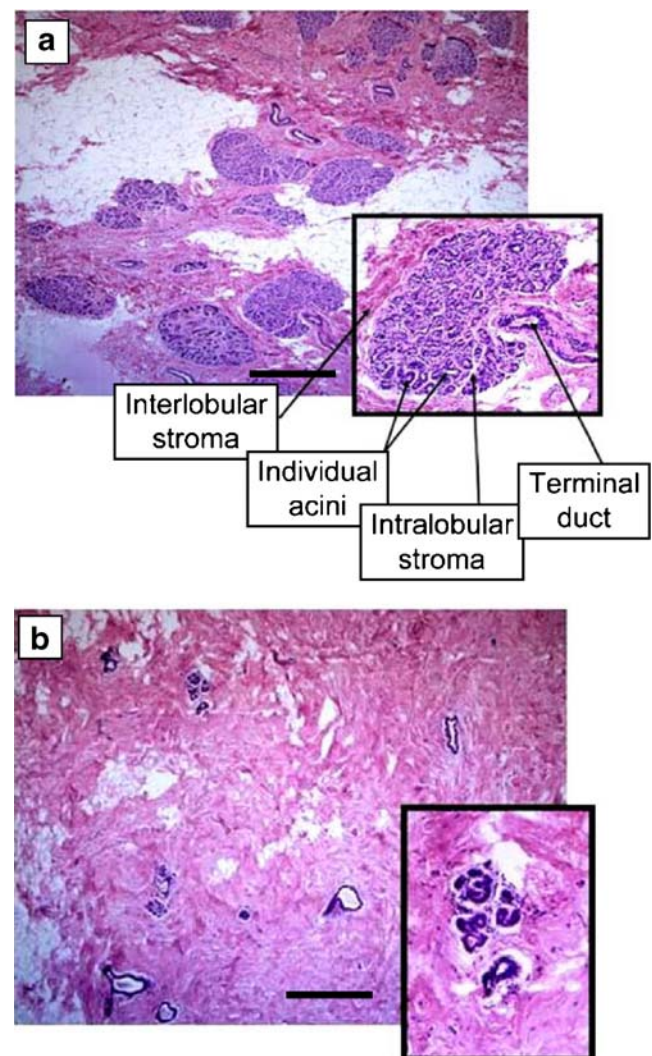

Figure 3 Histologic features of age-related lobular involution. **a** Noninvoluted breast tissue shows multiple, large terminal duct lobular units (TDLU) which contain numerous acini and which are separated from neighboring TDLU by specialized stroma. **b** Breast tissue with complete lobular involution shows scattered, sparse lobules containing few acini. Scale bars, 500 μm. Modified with permission from [4].
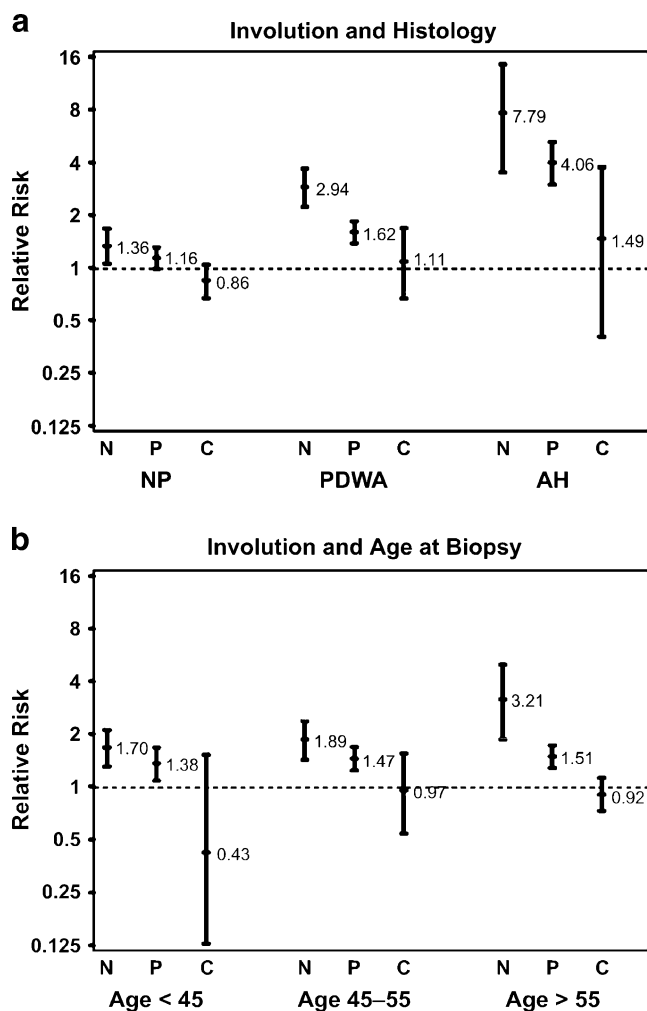
Figure 4 Association of breast cancer risk with lobular involution. Relative risks (as indicated) and their 95% confidence intervals (*error bars*) reflect the observed number of events compared with the number of expected events on the basis of Iowa Surveillance, Epidemiology, and End Results (SEER) data. All results account for the effects of age and calendar period. **a** Involution and histology. **b** Involution and age. N = no involution; P = partial involution; C = complete involution; NP = nonproliferative; PDWA = proliferative disease without atypia; AH = atypical hyperplasia. Reproduced with permission from [4].

that involution is contributing to this phenomenon [59]. The results of this study were recently corroborated in an analysis of patient samples from the Nurses' Health Study, which found that smaller lobular size was associated with decreased risk of cancer [60].

Conclusions and Future Directions

Investigations of postlactational involution using genetic mouse models have revealed an incredible complexity to the process: modulation of more than 50 different genes, through knockout or introduction of a breast-specific transgene, has

been found to delay or accelerate postlactational involution. That so many distinct molecular pathways are involved in regulation of postlactational involution in a nonredundant fashion indicates the complexity of this developmental process; that so many of the models also show a tumor developmental phenotype shows how deregulation of developmental pathways can be a stimulus for cancer development and progression. At present, the bulk of the evidence points to a correlation between delayed postlactational involution and increased cancer formation, suggesting tumor-promoting microenvironmental influences within the postlactational gland; this interpretation is consistent with the hypothesis that postlactational involution may underlie the phenomenon of pregnancy-associated breast cancer [17]. However, the corresponding expectation that premature involution should therefore be associated with decreased tumorigenesis is not as clear. It should be noted that the tumor phenotype has not been established for many genetic mouse models showing altered postlactational involution; a better understanding of the individual signals linking postlactational involution and tumorigenesis will likely follow from a better characterization of these models, as well as from characterization of postlactational defects in traditional mammary tumor models.

Lobular involution, while recognized as a physiological process for some time, has only recently been linked to cancer development. Unlike postlactational involution, very little is known about the signaling processes that control lobular involution, or even why lobular involution is associated with decreased cancer risk, although a simplistic possibility is that removal of epithelial cells eliminates the progenitor population for tumor formation. A curious aspect to the newly identified relationship between lobular involution and breast cancer is that lobular involution appears to be an age-related protective process. While cancer incidence usually increases with age, and so aging can be seen as a general risk factor, it appears that the failure of breast aging in postmenopausal women is related to increased risk of cancer development. Much additional research is required to understand how lobular involution is induced, why some women initiate lobular involution before menopause while others fail to undergo lobular involution even after menopause, and how lobular involution protects from breast cancer. A better understanding of these processes will help to inform individualized patient risk stratification, and may ultimately lead to medical interventions designed to induce lobular involution for the physiological prevention of breast cancer [59].

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