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REVIEW

Benign proliferative epithelial disorders of the breast: a review of the epidemiologic evidence

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Introduction

Benign breast disease (BBD) is a heterogeneous condition consisting of many histological entities [1], including ductal epithelial proliferations, adenomas and papillomas, and fibroadenomas [2]. Some of these lesions are thought to represent progressive changes in the stepwise sequence of histological changes leading to the development of breast cancer. Specifically, it has been hypothesized that non-atypical proliferative forms of BBD, proliferative disease with atypia, and in situ cancer represent successive steps preceding the development of invasive breast carcinoma [3]. This hypothesis is supported by experimental and epidemiologic evidence. Experimentally, xenografts of MCF10AneoT cells have been shown to progress from intraductal proliferative changes to lesions resembling atypical hyperplasia of the human breast and ultimately to lesions resembling carcinoma in situ [4]; this step-wise development of breast cancer has also been demonstrated using transgenic rat [5] and mouse [6] models. Epidemiologic studies have shown that women with proliferative epithelial disorders affecting the small ducts and the terminal ductal lobular units of the breast are at increased risk of subsequent breast cancer, particularly when the epithelial proliferation is accompanied by evidence of atypia [1, 7–9]. Risk is increased approximately 1.5–2 fold for those with epithelial proliferation without atypia [7–9] and 4–5 fold for those with proliferative disease with atypia [8, 10]. The higher risk associated with atypia is consistent with the notion that it is more proximal to carcinoma than proliferative disease without atypia. Given these findings, benign proliferative epithelial disorders (BPED) of the breast are considered to have malignant potential [11]. Our focus in the remainder of this review is on BPED of the breast.

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Descriptive epidemiology

It is difficult to estimate the prevalence and incidence of benign breast lesions in general, and of BPED of the breast in particular, since an unknown proportion of women with BBD come to clinical attention and proceed to biopsy [12]. Nevertheless, autopsy and epidemiological studies have provided estimates of the frequency of occurrence of BPED.

Several autopsy studies have provided data on the prevalence of benign proliferative epithelial disorders of the breast [13–23] at the time of death. The studies differed somewhat with respect to their use of histopathological terminology, perhaps accounting for the wide range of prevalence estimates, which extended from a low of 5–15% [13, 15] to a high of 64% [22]. The prevalence of BPED exceeded that of occult carcinoma of the breast substantially in most of these series, suggesting that even if benign proliferative epithelial disorders of the breast are precursors of breast cancer, they do not necessarily progress to cancer.

Currently, there are no published estimates of the incidence rate of BPED of the breast. However, incidence rates of broader groupings of BBD (e.g., fibrocystic disease or benign mammary dysplasia) have been shown with considerable consistency to increase rapidly with age until about 40–44 years, with peak incidence rates being

somewhere between 200 and 400/100,000/year, after which they decline rapidly [2, 24–28]. The disease remains relatively common after the menopause, with estimates of the annual incidence rate ranging from about 100/100,000 women in the early postmenopausal years to 20–30/100,000 women in the later postmenopausal years [29].

Etiology

There have now been several case–control [2, 30–53] and cohort studies [54–61] of the etiology of benign proliferative epithelial disorders of the breast. These studies have reported either on the risk of such lesions overall [2, 30–32, 34–41, 47–52, 54–57, 59, 62] or on risk by the degree of epithelial proliferation or cytological atypia displayed in the benign lesions [33, 34, 36, 37, 42–46], and they have generally focused on factors that have been studied in relation to the etiology of breast cancer. The rationale for this is that if BPED of the breast are indeed precursors of breast cancer, then BPED and breast cancer would be expected to have similar risk factors. At the very least, risk factors for the former would be expected to be a subset of those for the latter (since factors other than those responsible for the development of BPED might be responsible for the progression of BPED to breast cancer). In relation to the etiology of breast cancer, there is evidence to support an increased risk of breast cancer in association with a number of hormonal and reproductive factors including nulliparity, a relatively late age at first pregnancy, a relatively late age at natural menopause, and use of hormone replacement therapy [63]. In addition, there is evidence to support a positive association between ionizing radiation exposure, family history of breast cancer, alcohol consumption, and obesity in postmenopausal women [63]. In contrast, there is some evidence of an inverse association between physical activity, breast-feeding, and fruit and vegetable consumption and breast cancer risk [64, 65].

Hormonal and reproductive factors

Studies of hormonal and reproductive factors have focused on aspects of these exposures that have also been studied in relation to breast cancer, including age at menarche, parity, age at first birth, and use of exogenous hormones. The association between age at menarche and BPED of the breast has been investigated in nine case–control studies [2, 31, 33–35, 39–41, 53] and one cohort study [54], none of which has shown alterations in risk (Table 1). Of the studies that examined age at first birth [2, 30, 31, 33, 34, 40–42, 53, 54], two found statistically significant positive associations with older ages at first birth [30, 34] and one reported a 3-fold

Table 1 Association between age at menarche (years) and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Soini [2]	Case–control	Ductal epithelial hyperplasia	844 (422)	Finland	Mean age at menarche	No difference
Parazzini et al. [31]	Case–control	Dysplasia (ductal, other, mixed)	488 (203)	Italy	<14 vs. ≥14	[a]RR = 1.3 (0.9–1.9)
Bright et al. [35]	Case–control	Benign breast disease, all cases	306 (172)	United States	<13 vs. ≥13	RR = 0.69 (0.36–1.3)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (91)	Western Australia	Comparison of mean age (cases vs. controls)	No difference
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	14+ vs. ≤12	[b]OR = 0.7 (0.4 – 1.2)
Minami et al. [41]	Case–control	Proliferative benign breast disease	260 (130)	Japan	≥16 vs. ≤13	OR = 0.78 (0.39–1.53)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	≥17 vs. ≤13	OR = 0.8 (0.2–2.5)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	>13 vs. ≤13	OR = 1.35 (0.86–2.10)

[a] RR = relative risk, [b] OR = odds ratio

increase in risk among nulliparous women compared to women whose age at first birth was ≤24 years [41] (Table 2); the remaining seven studies found no association [2, 31, 33, 40, 42, 53, 54]. In relation to parity, only three [35, 41, 53] of 11 studies [2, 31, 33–35, 39–42, 53, 54] have supported an inverse association with risk, while the remaining studies observed no association (Table 3). There appears to be no association between either abortion [2, 34] or breast feeding history and risk [2, 41, 53, 54].

Several studies have also examined the etiological role of exogenous hormone use [35, 43–47, 54, 56]. Four studies, two cohort [54, 56] and two case–control [35, 43], have presented results for the association between oral contraceptive (OC) use and risk of BPED (Table 4), with two showing that risk of BPED was reduced in association with OC use [35, 56] and the others [43, 54] showing no association. Several other studies (all case–control) have reported on the association between OC use and risk of BBD by degree of histological atypia [42–46]. Findings for these studies have varied from those showing reduced risk of all grades of atypia [42] to those showing no reduction in risk with any grade of atypia [43]. With respect to hormone replacement therapy (HRT), while the cohort study by Rohan and Miller [47] observed a statistically significant increased risk of BPED in association with use of more than 8 years, earlier case–control studies, in which the association between HRT use and risk of BBD was examined by degree of histological atypia, found no evidence for a relationship [35, 46] (Table 5). In addition, a recent cohort study conducted by Friedenreich et al. [54] observed no association between HRT use and risk of BPED.

Family history

The literature regarding the association between family history of breast cancer and risk of BPED is mixed, with some studies finding a positive association BPED [34, 41] and others [33, 35, 39, 40, 53, 54] observing no association (Table 6).

Anthropometric and lifestyle factors

Several studies have examined weight and/or body mass index as risk factors. Of these studies, four have yielded findings suggesting an inverse association with either body weight [34, 39] or body mass index [31, 38] and five others have found no association [2, 33, 35, 40, 54] (Table 7). Only three of these studies, however, has examined this association by menopausal status [35, 40, 54]. Bright et al. [35], found a non-significant inverse association between obesity and BPED in both premenopausal (OR = 0.75,

Table 2 Association between age at first birth/pregnancy and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Soini [2]	Case–control	Ductal epithelial hyperplasia	844 (422)	Finland	Mean age at first birth	No difference
Lance [30]	Case–control	Proliferative benign breast disease	66 (33)	United States	≥25 vs. <25	[a]OR = 12 (2.43–59.30)
Parazzini et al. [31]	Case–control	Dysplasia (ductal, other, mixed)	570 (285)	Italy	≥30 vs. <20	OR = 1.8
Hsieh et al. [42]	Case–control	Fibrocystic disease with high atypia[b]	1,146 (218)	United States	Continuous (increase of 1 year)	OR = 0.85 (0.90–1.53)
Berkowitz et al. [33]	Case–control	Papillary hyperplasia with high atypia[c]	1,608 (590)	United States	Mean age at first birth (premenopausal women) vs. controls	No difference
					Mean age at first birth (premenopausal women) vs. controls	No difference
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	29+ vs. <21	OR = 1.0 (0.5–1.9)
Minami et al. [41]	Case–control	Proliferative benign breast disease	260 (130)	Japan	Nulliparous vs. ≤24	OR = 3.27 (1.37–7.78)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	≥32 vs. ≤24	OR = 0.3 (0.1–1.2)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	≥26 vs. nulliparous	OR = 1.27 (0.62 – 2.60)

[a] OR = odds ratio, [b] Outcome: mean ductal atypia score 2.375–3.000, [c] Outcome: mean ductal atypia score 2.30–3.00

Table 3 Association between parity and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Soini [2]	Case–control	Ductal epithelial hyperplasia	844 (422)	Finland	Mean number of births	No difference
Parazzini et al. [31]	Case–control	Dysplasia (ductal, other, mixed)	570 (285)	Italy	≥3 vs. nulliparous	[a]OR = 2.2
Hsieh et al. [42]	Case–control	Fibrocystic disease with high atypia	1,146 (218)	United States	Parity 3–4 vs. 1–2[c]	OR = 0.82 (0.18–3.71)
					Parity 5+ vs. 1-2[d]	OR = 1.06 (0.39–2.90)
Berkowitz et al. [33]	Case–control	Papillary hyperplasia with high atypia[e]	1,608 (590)	United States	Mean number of live births vs. controls (premenopausal women)	No difference
					Mean number of live births vs. controls (postmenopausal women)	No difference
Bright et al. [35]	Case–control	Proliferative benign breast disease without atypia	306 (172)	United States	Parous vs. nulliparous	[b]RR = (0.29 (0.12–0.71)
Ingram et al. [39]	Case–control	Proliferative benign breast disease	300 (99)	Western Australia	Comparison of mean parity (cases vs. controls)	No difference
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	3+ vs. nulliparous	OR = 1.0 (0.5–1.9)
Minami et al. [41]	Case–control	Proliferative benign breast disease	260 (130)	Japan	≥3 vs. nulliparous	OR = 0.29 (0.12–0.69)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	≥3 vs. nulliparous	OR = 0.1 (0.02–0.6)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	Parous vs. nulliparous	OR = 1.24 (0.62–2.51)
					≥4 vs. nulliparous	OR = 1.44 (0.71–2.93)

[a] OR = odds ratio, [b] RR = relative risk, [c] Outcome: mean ductal atypia score 2.375–3.000,[d] Outcome: mean ductal atypia score 1.875–2.250, [e] Outcome: mean ductal atypia score 2.30–3.00

Table 4 Association between oral contraceptive use and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Rohan et al. [43]	Case–control	Proliferative benign breast disease	575 (383)	South Australia	Ever vs. never	[d]OR = 0.9 (0.5–1.5)
					≥96 months vs. never	OR = 0.9 (0.4–1.9)
					≥30 vs. <20 years old at first use	OR = 0.9 (0.4–1.7)
Rohan and Miller [56]	Case-cohort	Proliferative benign breast disease	7,454 (2,116)	NBSS	Ever vs. never	[e]IRR = 0.92 (0.77–1.10)
					≥85 months vs. never	IRR = 0.68 (0.51–0.90)
					≥16 years since last use vs. never	IRR = 1.04 (0.80–1.35)
Li Volsi et al. [44]	Case–control	Fibrocystic disease with high atypia[a]	410 (205)	United States	Ever vs. never	OR = 3.00 (P_{trend} = 0.2)
Pastides et al. [45]	Case–control	Fibrocystic disease with high atypia[b]	1,045 (255)	United States	Ever vs. never	OR = 0.7 (ns)
					Mean duration of use in months (SE) for cases vs. controls	No difference
Berkowitz et al. [32]	Case–control	Fibrocystic disease with high atypia[c]	1,608 (590)	United States	Ever vs. never	OR = 8.8 (1.8–41.8)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	>1 year vs. never	OR = 0.6 (0.01–4.8)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	Ever vs. never	OR = 0.98 (0.64–1.51)
Bright et al. [35]	Case–control	Proliferative benign breast disease	306 (172)	United States	Ever vs. never	[f]RR = 0.35 (0.16–0.76)

[a] Outcome: mean ductal atypia score 2.3–2.75, [b] Outcome: mean ductal atypia score 2.00–2.74, [c] Outcome: mean ductal atypia score 1.8–2.29, [d] OR = odds ratio, [e] IRR = incidence rate ratio, [f] RR = relative risk

Table 5 Association between use of hormone replacement therapy and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Berkowitz et al. [46]	Case–control	Fibrocystic disease with high atypia[a]	1,608 (590)	United States	Ever vs. never	[b]OR = 0.9 (0.2–5.1)
					≥5 years vs. never	OR = 3.0 (0.5–17.5)
Friedenreich et al. [54]	Case–control	Proliferative benign breast disease	382 (165)	Canada	Ever vs. never	OR = 1.18 (0.77–1.81)
					>4 vs. 0 years	OR = 1.29 (0.80–2.11)
Rohan and Miller [47]	Case–control	Proliferative benign breast disease	6,134 (691)	NBSS	Current vs. never	[c]IRR = 1.45 (1.00–2.11)
					≥97 vs. 0 months	IRR = 1.70 (1.06–2.72)
Bright et al. [35]	Case–control	Proliferative benign breast disease	306 (172)	United States	Ever vs. never	[d]RR = 0.69 (0.36–1.3)

[a] Outcome: mean ductal atypia score 2.30–2.75, [b] OR = odds ratio [c] IRR = incidence rate ratio, [d] RR = relative risk

Table 6 Association between family history of breast cancer and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Comparison of % first degree family history (cases vs. controls)	No difference
Bright et al. [35]	Case–control	Benign breast disease, all cases	306 (172)	United States	Yes vs. no	[a]RR = 1.1 (0.54–2.4)
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	Yes vs. no	[b]OR = 0.9 (0.5–1.6)
Minami et al. [41]	Case–control	Proliferative benign breast disease	260 (130)	Japan	Yes vs. no	OR = 4.13 (1.46–11.71)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	First degree family history yes vs. no	OR = 3.2 (0.04–63.2)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	Yes vs. no[c]	OR = 1.30 (0.24–1.48)

[a] RR = relative risk, [b] OR = odds ratio, [c] Maternal history of breast cancer

95% CI = 0.38–1.5) and postmenopausal women (OR = 0.86, 95% CI = 0.40–1.8). In contrast, Friedenreich et al. [54], in a study population including 93% postmenopausal women, reported a non-significant 12% increased risk for women with a BMI ≥29.5 vs. <22.9 (95% CI = 0.63–1.97). Similarly, London et al. [40] found that, among postmenopausal women, there was a 30% increased risk of BPED for those who weighted >165 lbs compared to women who weighed <124 lbs. Given that BMI is positively associated with breast cancer risk among postmenopausal women, and there is some evidence that BMI may be inversely associated with risk in premenopausal women [66–68], it is possible that the conflicting data are due to the lack of stratification by menopausal status in the majority of these studies. To date, only two studies have examined the role of physical activity; in each of these studies there was no association with risk [52, 54].

Several studies have also examined lifestyle factors such as diet, alcohol consumption and cigarette smoking [32, 33, 36, 37, 39, 40, 48–50, 53–55, 57, 58, 60–62]. Of these studies, none of those which examined smoking history showed an association with risk [32, 33, 37, 54, 57, 61] (Table 8). Four studies have examined the association between alcohol consumption and risk. Of these, one [58] observed significant inverse associations between total alcohol intake and intake of wine and spirits, separately, and risk, while an earlier study [36] found no association (Table 9). More recently, a cohort studies by Friedenreich et al. [54] and Cui et al. [60] likewise observed no association between alcohol consumption and risk.

Aspects of diet have also been investigated in several studies as potential risk factors for BPED [38, 39, 47, 49, 50, 55, 59, 60, 62] (Table 10). While none of the studies to date support an association with total energy intake [48, 53, 55, 59], some studies have shown positive associations between saturated fat intake (or indices thereof) and risk of atypical [51] or proliferative forms [62] of BBD, although others [39, 48, 49, 55, 59] have provided little support for associations with dietary fat.

In relation to dietary fiber, Baghurst and Rohan [50] found strong inverse associations with total dietary fiber and its constituents (soluble and insoluble non-starch polysaccharides and cellulose). While these findings were supported to some extent by those of another study [39] in which risk of benign epithelial hyperplasia was reduced in association with consumption of fruit and leafy orange-red vegetables, others have observed no association between dietary fiber and risk [48, 55, 59]. Although Rohan et al. [48] provided some evidence for inverse associations between β-carotene intake and risk, a study by London et al. [40] showed that neither β-carotene nor retinol intake was associated with altered risk of atypical or non-atypical forms of BPED. Webb et al. [59] found no association

Table 7 Association between body mass index/weight/height and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Ingram et al. [38]	Case–control	Benign epithelial hyperplasia	307 (96)	Western Australia	>26 vs. ≤20	[a]OR = 0.27 (0.09–0.86)
Bright et al. [35]	Case–control	Benign breast disease, all cases	188 (125)	United States	Obese vs. non-obese[c]	[b]RR = 0.75 (0.38–1.5)
			118 (47)		Obese vs. non-obese[d]	[b]RR = 0.86 (0.40–1.8)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Comparison of mean BMI (cases vs. controls)	23.45 vs. 25.46 ($P < 0.05$)
					Comparison of mean weight (cases vs. controls)	62.1 vs. 64.2 kg ($P < 0.05$)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	≥29.5 vs. <22.9	OR = 1.12 (0.63–1.97)
					Weight gain since 18 ≥26.2 vs. <6.8 kg[e]	OR = 0.83 (0.46–1.50)
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	165+ vs. ≤124 lb[d]	OR = 1.3 (0.7–2.6)
Parazzini et al. [31]	Case–control	Dysplasia (ductal, other, mixed)	570 (285)	Italy	≥25 vs. ≤20	OR = 0.9
Soini et al. [2]	Case–control	Ductal epithelial hyperplasia	844 (422)	Finland	Mean weight	No difference
					Mean height	No difference
Berkowitz et al. [33]	Case–control	Fibrocystic breast disease	1,608 (590)	United States	≤25 vs. ≤20	OR = 0.4 (0.3–0.7)
Pastides et al. [34]	Case–control	Fibrocystic breast disease	1,015 (225)	United States	10 lb increase in weight women <55 years of age	OR = 0.8 (0.7–0.9)
					10 lb increase in weight women ≥55 years of age	OR = 1.0

[a] OR = odds ratio, [b] RR = relative risk, [c] premenopausal, [d] postmenopausal, [e] approximately 93% of study subjects were postmenopausal

Table 8 Association between smoking history and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	Ever vs. never smoker	[a]OR = 0.87 (0.57–1.31)
					≥15 vs. 0 pack years	OR = 0.75 (0.26–2.19)
Rohan et al. [37]	Case–control	Proliferative benign breast disease	575 (382)	South Australia, postmenopausal	Ever vs. never	[b]RR = 0.9 (0.6–1.2)
					Cigarette years ≥300 vs. never	RR = 1.7 (0.7–4.2)
Parazzini et al. [32]	Case–control	Dysplasia (ductal, other, mixed)	579 (288)	Italy	Ever vs. never	RR = 1.3 (0.5–3.1)
					Current vs. never	OR = 1.2 (0.8–1.8)
					Former vs. never	OR = 0.7 (0.4–1.3)
					≥10 vs. 0 cigarettes/day	OR = 1.0 (0.6–1.6)
					≥20 vs. 0 years smoking	OR = 1.4 (0.7–2.8)
Rohan [57]	Case-cohort	Proliferative benign breast disease	6,134 (691)	NBSS	Current vs. never	[c]IRR = 0.81 (0.64–1.03)
					Ex-smoker vs. never	IRR = 1.17 (0.97–1.41)
					Cigarette years >550 vs never	IRR = 0.92 (0.69–1.23)
Cui [61]	Prospective cohort	Proliferative benign breast disease	68,132 (1,792)	Women's health initiative	Ever vs. never	[d]HR = 0.97 (0.88–1.08)
					Ex-smoker vs. never	HR = 1.00 (0.90–1.11)
					Current vs. never	HR = 0.84 (0.69–1.02)

[a] OR = odds ratio, [b] RR = relative risk, [c] IRR = incidence rate ratio, [d] HR = hazard ratio

Table 9 Association between alcohol consumption and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Friedenreich et al. [54]	Nested case–control	Proliferative benign breast disease	382 (165)	Canada	Any vs. none	[a]OR = 1.15 (0.74–1.78)
					≥224 vs. 0	OR = 1.15 (0.69–1.91)
Rohan et al. [58]	Case-cohort	Proliferative benign breast disease	5,585 (557)	NBSS	≥30 vs. 0 g/day (total)	OR = 0.23 (0.13–0.40)
					≥10 vs. 0 g/day (beer)	OR = 0.76 (0.35–1.65)
					≥10 vs. 0 g/day (wine)	OR = 0.41 (0.26–0.66)
					≥10 vs. 0 g/day (spirits)	OR = 0.46 (0.31–0.71)
Rohan et al. [36]	Case–control	Proliferative benign breast disease	958 (383)	Australia	>10 vs. 0 g/day (total)	OR = 1.0 (0.6–1.7)
					≥10 vs. 0 g/day (beer)	[b]RR = 0.6 (0.3–1.3)
					≥10 vs. 0 g/day (wine)	RR = 0.7 (0.4–1.1)
					≥10 vs. 0 g/day (spirits)	RR = 0.9 (0.4–2.2)
Cui et al. [60]	Prospective cohort	Proliferative benign breast disease	68,132 (1,792)	Women's health initiative	Former vs. never	[c]HR = 1.02 (0.84–1.24)
					30 g/day vs. never	HR = 0.89 (0.63–1.26)

[a] OR = odds ratio, [b] RR = relative risk, [c] HR = hazard ratio

Table 10 Association between dietary factors and risk of BPED of the breast

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Energy						
Rohan et al. [55]	Case-cohort	Proliferative benign breast disease	5466 (545)	Canada	Q5 vs. Q1	[a]IRR = 0.90 (0.67–1.22)
Rohan et al. [48]	Case–control	Proliferative benign breast disease	575 (383)	South Australia	Q5 vs. Q1	[b]OR = 1.6 (0.9–3.0)
Wu et al. [53]	Case–control	Fibrocystic disease with atypia	1,130 (33)	China	>2,128 vs. <1,647.3 kcal	OR = 0.7 (0.2–1.9)
Webb et al. [59]	Prospective cohort	Proliferative benign breast disease without atypia	58,628 (786)	United States	≥2,128 vs. ≤1,390 kcal	[c]RR = 0.93 (0.76–1.14)
Fat						
Lubin et al. [51]	Case–control	Atypical benign breast disease grade 3+	2,332 (854)	Israel	Q4 vs. Q1 saturated fat (surgical controls)	OR = 3.6 (1.4–9.4)
					Q4 vs. Q1 saturated fat (neighborhood controls)	OR = 3.8 (1.3–10.7)
Hislop et al. [62]	Case–control	Proliferative benign breast disease	248 (124)	Canada	Frequent vs. rare intake (meat fat)	OR = 1.49 (0.66–3.36)
					Frequent vs. rare intake (dairy fat)	OR = 0.72 (0.34–1.53)
Rohan et al. [48]	Case–control	Proliferative benign breast disease	575 (383)	South Australia	Q5 vs. Q1 (total fat)	OR = 2.1 (1.2–3.8)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Median consumption	OR = 0.8 (0.5–1.6)
London et al. [49]	Case–control	Proliferative benign breast disease without atypia	573 (176)	United States	Q5 vs. Q1 (total fat)	OR = 1.2 (0.6–2.6)
Rohan et al. [55]	Case-cohort	Proliferative benign breast disease	5,466 (545)	Canada	Q5 vs. Q1	IRR = 0.88 (0.65–1.20)
Webb et al. [59]	Prospective cohort	Proliferative benign breast disease without atypia	58,628 (786)	United States	≥70 vs. ≤55.7 g	RR = 1.01 (0.83–1.23)
Dietary fiber						
Baghurst and Rohan [50]	Case–control	Proliferative benign breast disease	708 (354)	South Australia	Q5 vs. Q1 (community controls)	OR = 0.64 (0.34–1.19)
					Q5 vs. Q1 (biopsy negative controls)	OR = 0.45 (0.24–0.82)
Rohan et al. [55]	Case-cohort	Proliferative benign breast disease	5,466 (545)	Canada	Q5 vs. Q1	IRR = 1.11 (0.82–1.50)
Rohan et al. [48]	Case–control	Proliferative benign breast disease	575 (383)	South Australia	Q5 vs. Q1	OR = 1.4 (0.8–2.9)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Median consumption	OR = 0.8 (0.5–1.5)
Webb et al. [59]	Prospective Cohort	Proliferative benign breast disease without atypia	58,628 (786)	United States	≥21.1 vs. ≤14.7 g	RR = 0.99 (0.81–1.21)
Fruits & vegetables						
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Median consumption (fruit)	OR = 0.8 (0.4–1.5)
					Median consumption (vegetables)	OR = 1.2 (0.7–2.1)

Table 10 continued

Reference	Study design	Case definition	Number of study participants (No. cases)	Population (source)	Comparison	Risk estimate (95% CI)
Retinol/β-carotene/vitamin E/folate						
Rohan et al. [48]	Case–control	Proliferative benign breast disease	575 (383)	South Australia	Q5 vs. Q1 (retinol)	OR = 1.1 (0.6–2.0)
					Q5 vs. Q1 (β-carotene)	OR = 0.8 (0.4–1.4)
Rohan et al. [55]	Case-cohort	Proliferative benign breast disease	5,466 (545)	NBSS	Q5 vs. Q1 (retinol)	OR = 0.97 (0.71–1.31)
					Q5 vs. Q1 (β-carotene)	OR = 0.94 (0.70–1.27)
London et al. [40]	Case–control	Proliferative benign breast disease without atypia	576 (173)	United States	Q5 vs. Q1 (retinol)	OR = 0.8 (0.4–1.7)
					Q5 vs. Q1 (carotene)	OR = 1.5 (0.7–3.5)
					Q5 vs. Q1 (Vitamin E)	OR = 1.5 (0.7–3.4)
Ingram et al. [39]	Case–control	Benign epithelial hyperplasia	300 (99)	Western Australia	Median consumption (retinol)	OR = 1.2 (0.6–2.1)
					Median consumption (β-carotene)	OR = 0.9 (0.5–1.7)
Webb et al. [59]	Prospective cohort	Proliferative benign breast disease without atypia	58,628 (786)	United States	≥2,525 vs. ≤1,130 equivalents of vitamin A μg (retinol)	RR = 1.07 (0.85–1.34)
					>16.2 vs <7.7 mg (vitamin E)	RR = 0.84 (0.65–1.09)
Cui et al. [60]	Prospective cohort	Proliferative benign breast disease	68,132 (1,792)	Women's health initiative	>748 vs. <351 μg/day (folate-all sources)	[d]HR = 1.04 (0.91–1.20)
					>430 vs. <320 μg/day (folate-diet)	HR = 1.09 (0.95–1.25)
					Supplement use yes vs. no	HR = 1.00 (0.91–1.11)
Calcium						
Rohan et al. [55]	Case-cohort	Proliferative benign breast disease	5,466 (545)	NBSS	Q5 vs. Q1	IRR = 0.81 (0.60–1.07)

[a] IRR = incidence rate ratio, [b] OR = odds ratio, [c] RR = relative risk, [d] HR = hazard ratio

between either carotene or vitamin A consumption and risk of proliferative BBD without atypia or of atypical hyperplasia. Recently, Cui et al. [60] found no association between dietary or supplemental folate and risk of either non-atypical BPED or atypical hyperplasia.

Conclusion

Epidemiologic studies have shown that women with benign proliferative epithelial disorders of the breast are at increased risk of subsequent breast cancer [1, 7, 8], and it has been hypothesized that BPED of the breast may be pre-malignant lesions [29]. To date, studies of the etiology of BPED of the breast have revealed both differences and similarities to that of breast cancer. For example, although younger age at menarche has been shown to be associated with an increased risk of breast cancer [63], none of the studies that have examined age at menarche in relation to risk of BPED have found an association. Similarly, there does not appear to be any association between age at first birth/pregnancy and BPED risk, while this is an established risk factor for breast cancer [63]. In addition, most studies have observed no association between oral contraceptive use [43–45, 54] and risk of BPED, while OC use is a probable risk factor for breast cancer [63]. In contrast, there is some evidence of that both BPED and breast cancer are positively associated with hormone replacement therapy [46, 47, 63] and inversely associated with parity [35, 41, 63]. Discrepancies between reported risk factors for BPED and those for breast cancer are not surprising, given the selection bias and misclassification of outcome to which studies of the former are prone [1]. This limitation suggests that further advances in elucidating the epidemiology of BPED of the breast may come from prospective studies conducted in screened populations and using standard schemes for the classification of BPED. However, given the methodologic challenges, epidemiologic approaches seem unlikely to be able to confirm that BPED of the breast are breast cancer precursors. In contrast, molecular studies may shed further light on the BPED-breast cancer relationship if they can demonstrate that human breast cancers arise from clonal outgrowths of pre-existing benign lesions, such as BPED. Nevertheless, even in the absence of such information, the currently available evidence suggests that women with BPED of the breast warrant regular surveillance given the increase in subsequent breast cancer risk that they experience.

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