Factors influencing the effect of age on prognosis in breast cancer: population based study

Niels Kroman, Maj-Britt Jensen, Jan Wohlfahrt, Henning T Mouridsen, Per Kragh Andersen, Mads Melbye

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Department of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, DK 2300 Copenhagen, Denmark

Niels Kroman *senior registrar*

Jan Wohlfahrt *senior statistician*

Mads Melbye, *professor*

Danish Breast Cancer Cooperative Group, Rigshospitalet, DK 2100 Copenhagen, Denmark

Maj-Britt Jensen *statistician*

Henning T Mouridsen *consultant oncologist*

Department of Biostatistics, University of Copenhagen, DK 2200 Copenhagen, Denmark

Per Kragh Andersen *professor*

Correspondence to: M Melbye mme@ssi.dk

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Abstract

Objective To investigate whether young age at diagnosis is a negative prognostic factor in primary breast cancer and how stage of disease at diagnosis and treatment influences such an association.
Design Retrospective cohort study based on a population based database of patients with breast cancer containing detailed information on tumour characteristics, treatment regimens, and survival.
Setting Denmark.
Subjects 10 356 women with primary breast cancer who were less than 50 years old at diagnosis.
Main outcome measures Relative risk of dying within the first 10 years after diagnosis according to age at diagnosis after adjustment for known prognostic factors and expected mortality.
Results Overall, young women with low risk disease who did not receive adjuvant treatment had a significantly increased risk of dying; risk increased with decreasing age at diagnosis (adjusted relative risk: 45-49 years (reference): 1; 40-44 years: 1.12 (95% confidence interval 0.89 to 1.40); 35-39 years: 1.40 (1.10 to 1.78); <35 years: 2.18 (1.64 to 2.89). However, no similar trend was seen in patients who received adjuvant cytotoxic treatment. The increased risk in younger women who did not receive adjuvant treatment compared with those who did remained when women were grouped according to presence of node negative disease and by tumour size.
Conclusion The negative prognostic effect of young age is almost exclusively seen in women diagnosed with low risk disease who did not receive adjuvant cytotoxic treatment. These results suggest that young women with breast cancer, on the basis of age alone, should be regarded as high risk patients and be given adjuvant cytotoxic treatment.

Introduction

Women diagnosed with breast cancer in their 20s and 30s seem to have a poorer prognosis than women diagnosed in middle age.[1–7] The reason for this unusual pattern is unclear. Young women with breast cancer are more likely to have affected lymph nodes, be negative for oestrogen receptors, and have tumours that are large with a high grade of anaplasia [1–3] Thus, the poorer outcome could at least partly be due to differences in these important prognostic factors, although many, though not all, studies retain a negative effect after adjustment for such confounding factors.[1 8–19] It is unknown to what extent adjuvant cytotoxic treatment might influence this association.

We examined the effect of age on breast cancer survival adjusted for expected mortality using Denmark's large and very complete population based breast cancer registries. These include detailed information on clinical presentation, postoperative treatment, and follow up status for women with breast cancer. Our main objectives were to determine whether the poor prognosis reported among young women was independent of common prognostic factors and to what extent this pattern might be affected by treatment.

Subjects and methods

Population database

In 1977, the Danish Breast Cancer Cooperative Group (DBCG) started nationwide prospective studies on treatment of breast cancer.[20] Three programmes have so far been launched: DBCG 77 (patient accrual from 1977-82), DBCG 82 (patient accrual from 1982-9), and DBCG 89 (patient accrual since 1989). Primary clinical and histopathological data and data on postoperative treatment and status at follow up visits have all been registered by the Danish Breast Cancer Cooperative Group based on specific forms submitted by departments of surgery, pathology, and oncology in Denmark. Linkage between the Danish Breast Cancer Cooperative Group register and the Danish cancer registry, which is considered almost complete regarding reporting of breast cancer diagnoses among residents in Denmark,[21] showed a 94% concordance (unpublished result).

Patient records in the Danish Breast Cancer Cooperative Group registry were linked with the Danish civil registration system registry to obtain complete information on deaths. Since 1968, the civil registration system registry has assigned a unique identification number to all residents in Denmark. Individual information is kept under this personal identification number in all national registries, permitting accurate linkage of information in different registries. The civil registration system registry keeps updated files on dates of childbirth and death. A detailed description of the information included in this registry is given elsewhere.[22]

Recent studies have shown that age at first birth and short interval between last birth and diagnosis of breast cancer may affect the prognosis of breast cancer.[23 24] Information on childbirth history was available for women born since 1 April 1935.

Treatments

Patients were classified as either low or high risk according to histopathological criteria. Detailed information on allocation of risk groups is given elsewhere.[23] For all three programmes, the primary surgical treatment of patients was total mastectomy plus axillary dissection (90% of the population) or lumpectomy with axillary dissection. Standard adjuvant cytotoxic chemotherapy was used in all three pro-

Table 1 Postoperative adjuvant treatment given during 1977-96 to Danish premenopausal women with high risk breast cancer

Treatment protocol	Treatment randomisation
DBCG 77	Radiotherapy *or*
	Radiotherapy plus levamisol *or*
	Radiotherapy plus cyclophosphamide *or*
	Radiotherapy plus CMF
DBCG 82	CMF *or*
	CMF plus radiotherapy *or*
	CMF plus tamoxifen
DBCG 89:	
Oestrogen receptor positive	CMF *or*
	Castration
Oestrogen receptor negative	CMF *or*
	CEF *or*
	CMF plus pamidronate *or*
	CEF plus pamidronate

CMF=cyclophosphamide plus methotrexate plus fluorouracil.
CEF=cyclophosphamide plus epirubicin plus fluorouracil.

grammes.[20 25] Table 1 gives a summary of the adjuvant treatment.

Patients with bilateral breast cancer or inflammatory cancer, distant metastases, contraindications to the planned postoperative treatment, or who were not treated according to the surgical guidelines were not allocated to any of the protocols.

Statistical analysis

Women who had breast cancer diagnosed between January 1978 and 1 July 1996 were included and followed up for 10 years after diagnosis or until 1 July 1996, whichever came first, with respect to survival. The study was restricted to premenopausal women aged younger than 50 at the time of diagnosis.

The overall death rate was modelled by a sum of two terms. The first term was the age and calendar specific expected mortality as a known time dependent offset. Expected mortality was obtained from life tables for the total female population in Denmark in five year age groups and five year calendar periods.[26] The second term in the overall model was the exponential function of a linear expression including the categorical variables age at diagnosis (five year groups), tumour size ($\leq$2 cm, $>$2-5 cm, $>$5 cm), number of positive nodes (0, 1-3, 4-9, $\geq$10), histological grading (I, II and III, non-ductal carcinomas), protocol allocation (allocated, not treated according to surgical guidelines, not allocated for other reasons), and year of diagnosis (1977-81, 1982-88, 1989-96). This model can be viewed as a log-linear model of the observed death rate minus the expected death rate—that is, a log-linear model of the excess death rate. The expected number of deaths due to breast cancer amounts to only a small proportion of all expected deaths.[26] Therefore, the adjusted relative risks were interpreted as relative risks of death due to breast cancer. Poisson regression was chosen instead of Cox regression to facilitate additive adjustment for expected mortality.

We also did multivariate analyses without adjusting for expected mortality, which allowed us to use both Poisson and Cox regression. The two approaches gave identical estimates of the relative risk. All tests in the Poisson regression analyses were performed as likelihood ratio tests with Epicure.[27] Tests for difference in the age effect in low risk patients compared with high risk patients receiving cytotoxic treatment were performed by including an interaction term between age and risk group. Association between age at diagnosis and tumour characteristics was analysed by χ^2 tests.

Results

By 1 July 1996, 10 356 premenopausal women aged younger than 50 with primary breast cancer were registered with the Danish Breast Cancer Cooperative Group. Our cohort represented a total of 52 432 person-years of follow up. Table 2 shows the distribution of patients according to tumour characteristics, protocol allocation, and age at diagnosis. Compared with older patients, patients aged younger than 35 at diagnosis were at higher risk of being node positive (51% (404/795) *v* 46% (4061/8854); P = 0.02). The proportion of patients with histological grading I was significantly lower in patients aged younger than 35 compared with older patients (18% (122/668) *v* 32% (2321/7303); P < 0.001).

To evaluate the independent effect of age at diagnosis on survival from breast cancer, we performed a multivariate analysis that included age at diagnosis, tumour size, axillary nodal status, histological grading, year of treatment, protocol allocation, and expected mortality (table 3). Women aged 45-49 years were chosen as the reference category because they constituted the largest group around the time of menopause. Compared with this group, women in the two age groups less than 40 years at diagnosis were at significantly increased risk of dying (table 3). Women younger than 35 had the worst prognosis, with a

Table 2 Distribution of 10 356 premenopausal women with primary breast cancer operated on in Denmark during 1977-96 according to tumour characteristics, risk group allocation, and age at diagnosis. Values are numbers (percentages)

	Age at diagnosis (years)			
	<35 (n=867)	35-39 (n=1733)	40-44 (n=3354)	45-49 (n=4402)
Tumour size (cm):				
≤2	431 (49.7)	948 (54.7)	1769 (52.7)	2322 (52.8)
>2-5	330 (38.1)	595 (34.3)	1169 (34.9)	1652 (37.5)
>5	69 (8.0)	133 (7.7)	278 (8.3)	291 (6.6)
No information	37 (4.3)	57 (3.3)	138 (4.1)	137 (3.1)
No of positive nodes:				
0	391 (45.1)	886 (51.1)	1691 (50.4)	2216 (50.3)
1-3	259 (29.9)	478 (27.6)	910 (27.1)	1258 (28.6)
4-9	114 (13.1)	174 (10.0)	397 (11.8)	497 (11.3)
≥10	31 (3.6)	76 (4.4)	127 (3.8)	144 (3.3)
No information	72 (8.3)	119 (6.9)	229 (6.8)	287 (6.5)
Histological grading:				
I	122 (14.1)	351 (20.3)	812 (24.2)	1158 (26.3)
II and III	546 (63.0)	1017 (58.7)	1785 (53.2)	2180 (49.5)
Non-ductal carcinoma*	199 (23.0)	365 (21.1)	757 (22.6)	1064 (24.2)
Oestrogen receptor status†:				
Positive	198 (51.2)	469 (57.8)	1086 (65.9)	1634 (71.0)
Negative	189 (48.8)	342 (42.2)	561 (34.1)	667 (29.0)
Risk group:				
Low	315 (36.3)	733 (42.3)	1423 (42.4)	1920 (43.6)
High	349 (40.3)	677 (39.1)	1319 (39.3)	1715 (39.0)
Not treated according to guidelines‡	143 (16.5)	231 (13.3)	443 (13.2)	496 (11.3)
Not allocated for other reasons§	60 (6.9)	92 (5.3)	169 (5.0)	271 (6.2)

*Includes women with no information available on histological grading.
†Information available for 5146 (49.7%) women.
‡Patients not allocated because surgical treatment did not follow guidelines.
§Patients not allocated because of medical contraindications, bilateral or inflammatory breast cancer, or distant metastases.

Table 3 Adjusted relative risk of dying after diagnosis of primary breast cancer according to age at diagnosis, tumour characteristics, and protocol allocation in 9541 breast cancer patients* diagnosed during 1978-96

Variables	Adjusted relative risk (95% CI)†
Age at diagnosis (years):	
<35	1.46 (1.27 to 1.70)
35-39	1.26 (1.12 to 1.42)
40-44	1.07 (0.97 to 1.19)
45-49	1 (reference)
Tumour size (cm):	
≤2	1 (reference)
>2-5	1.78 (1.61 to 1.97)
>5	2.31 (2.00 to 2.67)
No of positive nodes:	
0	1 (reference)
1-3	1.80 (1.62 to 2.01)
4-9	3.44 (3.05 to 3.89)
≥10	4.71 (3.96 to 5.59)
Histological grading:	
I	1 (reference)
II and III	2.44 (2.12 to 2.81)
Non-ductal carcinoma‡	1.12 (1.00 to 1.43)
Protocol allocation:	
Allocated	1 (reference)
Not treated according to surgical guidelines	1.11 (0.95 to 1.28)
Not allocated for other reasons§	2.61 (2.26 to 3.01)

*815 patients (7.9%) excluded because of missing information on tumour size or nodal status.
†Adjusted for age at diagnosis, tumour characteristics, protocol allocation, year of diagnosis, and expected mortality.
‡Includes patients with no information on histological grading.
§Medical contraindications, bilateral or inflammatory breast cancer, or distant metastases.

1.46-fold increased risk of dying. The results were not changed by adjustment for oestrogen receptor status in the subgroup of patients for whom this information was available (data not shown).

To evaluate the effect of adjuvant cytotoxic therapy in relation to age at diagnosis, we allowed for an interaction between age at diagnosis and low risk patients (none of whom received adjuvant treatment, n = 4329), versus high risk patients (all of whom received adjuvant cytotoxic treatment, n = 2824; figure). Among patients who did not receive adjuvant cytotoxic treatment, there was a highly significant increased risk of dying with decreasing age (adjusted relative risk: 45-49 years: 1 (reference); 40-44 years: 1.12 (95% confidence interval 0.89 to 1.40); 35-39 years: 1.40 (1.10 to 1.78); <35 years: 2.18 (1.64 to 2.89). A similar trend was not observed in young patients receiving adjuvant cytotoxic therapy (high risk disease) (see figure). The negative effect of young age among women without adjuvant cytotoxic treatment was significantly more pronounced than that observed in the group of treated patients (test for effect modification: P = 0.02).

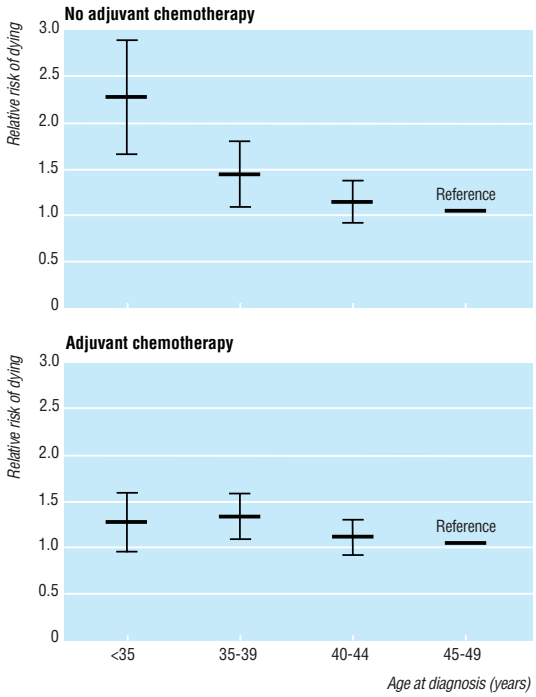
In further analyses we looked at the effect of treatment among node negative women (table 4). In line with the findings above, only young women in the group that received no treatment were at increased risk; no increased risk was observed among women who received adjuvant cytotoxic treatment. A similar pattern was observed when the analysis was restricted to women with small tumours at diagnosis (≤2 cm) or women with large tumours (>2 cm).

We have previously shown that age at first childbirth and time since last birth are independent prognostic factors for death from breast cancer.[23 24] Complete information on reproductive history was available for 3373 low risk patients (77.9%). The estimated prognostic effect of age at diagnosis was not significantly altered by adjusting for age at first childbirth or time since last birth (data not shown).

Discussion

In agreement with previous studies, we found that breast cancer in young women has a particularly poor prognosis.[1 4–19] Younger women are at high risk of having axillary lymph node disease and tumours with high histopathological grading and of being oestrogen receptor negative.[1–3]

Part of the explanation for young women having more advanced and aggressive disease at diagnosis has been suggested to be the increased potential for a delayed diagnosis.[17 28] Detecting tumours in the breasts of young women is difficult because of the density of the mammary glands, and this problem is particularly pronounced among pregnant and lactating women.[29] Our detailed information on tumour characteristics at diagnosis enabled us to adjust for the effect of factors such as tumour size, nodal status, and histological grading and therefore judge more clearly the independent effect of age. Furthermore, we had complete reproductive history for a subset of the women and could therefore include the previously reported negative prognostic effect of a recent childbirth in our multivariate analyses. However, none



Adjusted relative risk of dying after diagnosis of primary breast cancer according to age at diagnosis among 4329 low risk patients who received no adjuvant treatment (top) and 2824 high risk patients who received adjuvant cytotoxic treatment (bottom). Women aged 45-49 at diagnosis were used as reference. Bars indicate 95% confidence intervals. Relative risk was adjusted for tumour size, nodal status, histological grading, year of diagnosis, and expected mortality

Table 4 Adjusted relative risk (95% confidence interval) of dying according to age at diagnosis and treatment in node negative women and women with tumour size ≤2 cm and >2 cm

Age at diagnosis (years)	Node negative*		Tumour size ≤2 cm		Tumour size >2 cm	
	No adjuvant treatment	Adjuvant cytotoxic treatment	No adjuvant treatment	Adjuvant cytotoxic treatment	No adjuvant treatment	Adjuvant cytotoxic treatment
<35	2.1 (1.6 to 2.8)	0.6 (0.1 to 5.5)	2.8 (1.9 to 4.0)	1.3 (0.9 to 2.1)	1.5 (1.0 to 2.4)	1.2 (0.9 to 1.6)
35-39	1.4 (1.1 to 1.7)	0.9 (0.3 to 3.5)	1.4 (1.0 to 1.9)	1.3 (0.9 to 1.9)	1.4 (1.0 to 2.0)	1.3 (1.0 to 1.6)
40-44	1.1 (0.9 to 1.4)	0.7 (0.2 to 2.3)	1.1 (0.8 to 1.5)	1.1 (0.8 to 1.5)	1.1 (0.8 to 1.5)	1.1 (0.9 to 1.3)
45-49†	1	1	1	1	1	1

*Only node negative women were considered in the analysis as all node positive women received adjuvant cytotoxic treatment.
†Reference group.

of these adjustments changed the overall result that young age at time of diagnosis is associated with a particularly poor prognosis. This argues in favour of breast cancers among young women tending to be biologically more aggressive than those diagnosed in older women but does not indicate how these cancers respond to adjuvant cytotoxic chemotherapy. However, other results suggest that tumours in young women respond adequately to chemotherapy. A meta-analysis of 133 randomised trials including 75 000 women with high risk breast cancer found the relative benefit of adjuvant cytotoxic chemotherapy to be larger in patients younger than 50 years compared with patients older than 50.[30]

Treatment of younger women

Henderson and Patek have argued against accepting young age alone as a criterion for adjuvant treatment.[31] The international consensus panel on the treatment of primary breast cancer came to a similar conclusion in 1995,[32] but has recently changed its recommendation to include women younger than 35, although no scientific evidence to back this decision was presented.[33] To evaluate the role of postoperative adjuvant cytotoxic treatment in relation to age at diagnosis we allowed for an interaction between age at diagnosis and low risk patients who received no adjuvant treatment versus high risk patients who received adjuvant cytotoxic treatment. We found that the negative effect of young age was almost exclusively seen in women classified as having low risk disease, being non-significant in high risk patients who received cytotoxic adjuvant treatment. This finding remained when the comparison of women who did and did not receive adjuvant cytotoxic treatment was restricted to node negative patients and patients with the same tumour size. This raises the question of whether the negative effect of young age seen in low risk patients is due to lack of adjuvant cytotoxic treatment. Our results cannot be taken as direct evidence that young patients classified as having low risk disease will benefit from adjuvant cytotoxic treatment. However, Fisher et al recently showed that women with low risk disease do benefit from adjuvant cytotoxic treatment and that the greatest benefit is seen in premenopausal women.[34] Therefore, we feel confident that the low risk tumours associated with a poor prognosis in young women will respond to adjuvant cytotoxic treatment leading to a better prognosis for this group of women.

The relative risk of dying was adjusted for expected mortality, which includes death from breast cancer. In some age categories, particularly among young women, this leads to an underestimation of the disease-specific risk because death from breast cancer accounts for up to 15% of the total mortality in young women.[26] Thus, the prognosis for young compared with middle aged women is probably worse than we estimated. However, this approach did not introduce an age differential bias when comparing the age specific effects in women receiving no treatment with those receiving adjuvant treatment.

In conclusion, we found that diagnosis of breast cancer at a young age was associated with an increased risk of death, with women younger than 35 at diagnosis having the worst prognosis of all age groups. The age effect was not significant among women who received adjuvant cytotoxic treatment, but was highly significant among low risk women who received no adjuvant treatment. These results suggest that all young women with breast cancer should be regarded as high risk patients and be offered adjuvant cytotoxic treatment.

What is already known on this subject

Most previous studies indicate that young age at diagnosis of breast cancer is an independent negative prognostic factor

No study has evaluated whether the negative effect of young age is influenced by adjuvant cytotoxic treatment

What this paper adds

This large population based study shows that the negative effect of young age occurs almost exclusively among those not receiving adjuvant treatment

Age did not have a significant effect among women who received adjuvant cytotoxic treatment

Young age should be considered as a sole criterion for allocating breast cancer patients to adjuvant cytotoxic treatment

Contributors: NK had the idea for the study, obtained the necessary permissions, and contributed to the planning and execution. MM participated in the planning, execution, and analysis and is guarantor of the work. JW and PKA participated in the planning and statistical execution of the study. MBJ did the statistical analysis. HTM had the idea for the study, took part in the design, and was essential to establishing the Danish Breast Cancer Cooperative Group register. NK and MM wrote the first draft of the paper, and all authors contributed to the final version.

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Commentary: much still to learn about relations between tumour biology, prognosis, and treatment outcome in early breast cancer

Andrew Tutt, Gillian Ross

Breakthrough Toby Robins Breast Cancer Research Centre, Institute of Cancer Research, London SW3 6JB
Andrew Tutt *Medical Research Council research training fellow*
Gillian Ross *senior lecturer in oncology*
Correspondence to: G Ross gillr@icr.ac.uk

What is it about breast cancer in women under 40 that is independently associated with worse prognosis? And what biological factors could explain both the poor prognosis and the disproportionately improved outcome seen after adjuvant chemotherapy? Do these tumours have special characteristics that can account for both these observations?

Possible mechanisms

Two biological processes could be implicated. The first involves changes in the ability of tumour cells to maintain the correct DNA sequence and to survive DNA damage caused by chemotherapy and radiotherapy. The second involves underlying molecular changes that promote rapid tumour proliferation.

The p53 protein acts to safeguard the integrity of the genetic code. If DNA is damaged and a cell proliferates without repair, mutations are passed on to daughter cells. Rapid acquisition of multiple mutations can lead to early onset aggressive cancers. Under normal circumstances the p53 protein prevents this by arresting the cell cycle to allow repair of damaged DNA or by promoting cellular suicide (apoptosis). A mutation in the p53 gene disrupts this normal DNA housekeeping, and cells can continue to proliferate unabated despite the presence of damaged DNA. Similarly, if the p53 protein is not functional the ability of cells to recognise and respond to damage induced by chemotherapy or radiotherapy may be reduced, potentially allowing tumour cells to survive cancer treatment.

The cell membrane receptor p185 is also involved in the control of cellular proliferation. It is encoded for by the gene c-erbB-2. When this receptor is activated, cell proliferation is stimulated. In many breast cancers c-erbB-2 is overexpressed, leading to increased cellular proliferation.

Evidence of action in breast cancer

Mutations in p53, overexpression of c-erbB-2, and high tumour proliferation are all associated with age under 40 years and with adverse prognosis in breast cancer.[1] When p53 status and tumour proliferation markers are included in multivariate analyses, age no longer remains an independent prognostic factor.[2] This suggests that these factors contribute significantly to the adverse prognostic effect of young age. But what evidence is there that these molecular phenotypes also modify response to treatment? The presence of mutated p53 is, as expected, associated with reduced benefit from adjuvant systemic treatment.[3] High tumour proliferation is at best of no predictive value or is indicative of worse response in locally advanced disease.[4] Similarly, overexpression of c-erbB-2 is associated with the development of resistance to tamoxifen and possibly reduced benefit from adjuvant systemic treatment.[5] Thus none of these three factors can be held responsible for both adverse prognosis and improved treatment outcome.

Other possible candidates to explain the phenomenon are the two breast cancer predisposition genes BRCA1 and 2. These proteins have a role in the repair of spontaneous DNA damage and that induced by radiotherapy and some chemotherapy drugs. Mutations in these genes may thus make tumour cells more responsive to treatment. However, since only 5.9% of women with breast cancer aged younger than 36 have germline mutation in these genes[6] and somatic mutations are not found in sporadic breast cancer, it is unlikely that Kroman et al's results can be explained by mutations in BRCA1 or 2. In addition, it remains to be shown whether BRCA1 or 2 mutant breast cancers are more responsive to radiotherapy or chemotherapy. Importantly, there is no evidence that mutation carriers have a worse prognosis than stage and grade matched controls.[7]

Future research

The biological explanations for Kroman et al's observations remain unclear. We require more information about the molecular pathology correlated with the effects of treatment on survival in large clinical trials. The development of cDNA microarray technology will soon allow us to analyse the differences in expression of thousands of genes in breast tumour specimens. This may show patterns of gene expression associated with early onset breast cancer and subsequent correlations with prognosis and outcome after treatment. It will then be critical to observe whether age remains an independent significant prognostic factor in women with small, low grade, node negative tumours, currently defined as low risk. Until this information is available, based on the results of this study, oncologists may rightly consider young age alone an indicator of poorer prognosis and a relative indication for adjuvant chemotherapy.

Competing interests: None declared.

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Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study

Peretz Lavie, Paula Herer, Victor Hoffstein

Abstract

Objective To assess whether sleep apnoea syndrome is an independent risk factor for hypertension.
Design Population study.
Setting Sleep clinic in Toronto.
Participants 2677 adults, aged 20-85 years, referred to the sleep clinic with suspected sleep apnoea syndrome.
Outcome measures Medical history, demographic data, morning and evening blood pressure, and whole night polysomnography.
Results Blood pressure and number of patients with hypertension increased linearly with severity of sleep apnoea, as shown by the apnoea-hypopnoea index. Multiple regression analysis of blood pressure levels of all patients not taking antihypertensives showed that apnoea was a significant predictor of both systolic and diastolic blood pressure after adjustment for age, body mass index, and sex. Multiple logistic regression showed that each additional apnoeic event per hour of sleep increased the odds of hypertension by about 1%, whereas each 10% decrease in nocturnal oxygen saturation increased the odds by 13%.
Conclusion Sleep apnoea syndrome is profoundly associated with hypertension independent of all relevant risk factors.

Sleep Laboratory, Bruce Rappaport Faculty of Medicine, Israel Institute of Technology, Haifa, Israel
Peretz Lavie *professor*
Paula Herer *statistician*

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Introduction

The strong association between obstructive sleep apnoea syndrome and hypertension has attracted con-