

Long-term Survival in Patients with Incurable Breast Cancer. An Analysis of 93 Cases

WALTER RHOMBERG¹ and THOMAS RHOMBERG²

¹Department of Radiooncology, General Hospital, Feldkirch, Austria;

²Department of Pharmacology, Medical University of Innsbruck, Innsbruck, Austria

Abstract. *Background/Aim:* The aim of this study was to elucidate why some patients with incurable breast cancer may survive far beyond our expectation. *Patients and Methods:* The analysis is based on two cohorts of patients with unresectable locoregional recurrences or distant metastases. Survival time, tumor characteristics, disease-free interval, metastasis type, coexistent diseases and a family history for breast cancer were recorded. *Results:* Among 553 patients, 93 patients were found to have survived >4 years. The following favourable prognostic factors were identified: a disease-free interval of 5.5 years and a high frequency of locoregional and skeletal metastasis. In addition, the patients showed several coexistent disorders and a higher incidence of familial breast cancer. The more coexistent disorders are found in a patient, the longer seems to be the survival. *Conclusion:* Survival in metastatic breast cancer may not only be determined by known prognostic factors but also by a variety of hormonal and complex genetic influences, and possibly by non-cytotoxic drugs.

Research on prognostic factors is a long data lasting request in oncology. It is important to have about subsets of patients with different natural histories of their disease if, e.g., treatment arms of randomized studies are to be compared. Moreover, a favourable prognosis facilitates the care of and the dialogue with a patient, and the decision for a more expensive treatment. Clinical research of this kind may also contribute to a better understanding of tumor biology. In case of metastases of breast cancer, the survival is dependent on certain parameters of the primary tumor (TNM-stage, grade, hormonal receptors), the disease-free interval (1) and the pattern of distant metastasis and the associated tumor burden.

Correspondence to: Prof. Dr. Walter Rhomberg, Department of Radiooncology, General Hospital, A-6700 Bludenz Unterfeldstrasse 32, Austria. Tel: +43 6643943043, e-mail: walter.rhomberg@gmx.at

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The median survival from metastatic breast cancer is 12 months without treatment (2). The use of modern cytotoxic and hormonal therapies has, of course, improved the life expectancy, which presently ranges between 12 and more than 24 months (2, 3). In earlier decades, roughly 10 to 15% of patients with disseminated breast cancer survived longer than 5 years (4) and in recent patient series, 5-year survival times around 20% were reported (5-7). The reasons why some patients survive far beyond the median survival are not yet clear. Since many years we were looking for patients with irresectable locoregional and/or metastatic breast cancer who survived longer than expected. The data of those patients were collected over the years and they were now analyzed with regard to various prognostic factors and comorbid conditions.

Patients and Methods

The data of patients with incurable, advanced breast cancer who survived more than 4 years have been prospectively collected between 1975 and 2000. This is a personal patient series, where most of the patients were treated by the first author once an unresectable locoregional recurrence or distant metastasis occurred. The women were treated by contemporary surgery, postoperative and palliative radiotherapy as well as with the latest cytotoxic and hormonal agents, according to the respective consensus of the international medical community. The analysis is based on two cohorts of patients with incurable breast cancer: 343 patients treated at the Department of Radiation Oncology of the Medical University of Hannover (Germany) from 1974 to 1979 and 210 patients treated at the Department of Radiation Oncology of the Federal Academic Hospital in Feldkirch (Austria) between 1985 and 2000. Among these 553 patients we found 93 patients (17%) who survived longer than 4 years from the occurrence of unresectable locoregional recurrences or distant metastasis. The TNM classification and histology of the primary tumor, the disease-free interval and the onset and type of recurrence were recorded. Diagnoses of concomitant diseases were taken over by the referring departments of surgery and internal medicine in the majority of cases. The work-up of the patients comprised complete blood counts and serum analyses with electrolytes, blood glucose, cholesterol, triglycerides, blood urea nitrogen (BUN), creatinine, enzymes and the tumor markers carcinoembryonic antigen (CEA) and cancer antigen 15-3

(Ca 15-3) during their treatment in the department of radiation oncology. Although *BRCA-1* and *BRCA-2* testing was available since 1995, these genetic parameters were not determined between 1995 and 2000 even in the case of a positive family history for breast cancer. Human epidermal growth factor receptor (HER-2) status was determined for the patients which were treated after 1995. The diagnoses of concomitant diseases such as type 2 diabetes were taken over by the referring departments. There was, as a rule, no prospective work-up related to metabolic diseases from our side apart from the cohort I patients who received oral glucose tolerance tests if diabetes mellitus was suspected.

Results

Altogether, 93 patients were identified to have survived beyond 4 years since the occurrence of unresectable locoregional disease or distant metastases. This subset of patients comprised 17% of the two cohorts observed. The length of the survival times of these patients is illustrated in Figure 1. The median age of the patients was 54 years (range=35-72). Twenty five patients were premenopausal, 55 were peri- and post-menopausal and in 13 cases the menopausal state was unknown.

Initial TNM classification and disease-free interval. The numbers of the initial TNM classification of the long-term survivors were as follows:

T1 N0: 6	T3 N1-3: 13
T1 N1: 4	T4 N1-3: 10
T2 N0: 14	Tx N1: 7
T2 N1: 20	Tx Nx: 16
T3 N0: 3	M1, any T or N: 9

The median disease-free interval from the diagnosis of the primary tumor to the onset of an unresectable locoregional recurrence or distant metastasis was 5.5 years (range=0-20 years).

Metastatic sites. There was a predominance of the locoregional and skeletal type of dissemination. The locoregional type was seen in 22 (24%) and the skeletal type in 34 patients (37%), respectively. The visceral dominant type was noted 9 times (10%) and a mixed-type of metastasis occurred in 27 cases (29%). Within the mixed forms of metastasis, the involvement of bones and visceral organs was noted in 11 cases, bones and soft tissues in 8 and regional plus visceral metastasis in 6 cases. Two cases showed an ubiquitous dissemination. One case was unknown with respect to the distribution of secondaries.

Family history of breast cancer. A family history of breast cancer was reported by 22 out of 89 patients (25%). First-degree relatives were involved in 15 and second degree relatives in 7 cases. The question of a positive family history was explicitly denied by 42 patients and in 4 cases no history

was taken in this respect. *BRCA-1* and *BRCA-2* gene analyses were not performed, the majority of patients have been treated before 1995.

Concurrent diseases and disorders. The most frequent concomitant diseases were type-2 diabetes mellitus (n=41), disorders of the lipid metabolism (n=37) and hyperuricemia (n=11) including 3 cases with typical symptoms of gout. Two patients of the latter group had kidney stones. Among the diabetic patients there were 12 with sub-clinical disease only. All concurrent diseases and co-morbidities are listed in Table I.

Survival times in relation to coexistent disorders. Eighteen patients showed neither a positive family history for breast cancer nor any concomitant disease. The mean survival time of these 18 patients was 5.3 years (range=4-9); two of these survived 7 years, there were no 10-year survivors.

If the cases were associated with a positive history for breast cancer and/or one or more of the features listed in Table I, the chance for a long-term survival increased. The more aberrations found in a patient, the longer their survival. Type 2 diabetes mellitus, disorders of the lipid metabolism and a positive family history for breast cancer were most frequently found as concomitant features.

The mean survival, in association with 1 or 2 features, was 5.9 years (range=4-10 years) and 6.9 years (range=4-17), respectively. If 3 or more coexistent disorders with or without a positive family history for breast cancer were found (12 patients), the mean survival was 8 years (range, 4-18). Eight out of the 12 patients (67%) survived longer than 7 years. The results are further illustrated in Figure 2.

Discussion

A group of 93 patients with incurable breast cancer that survived longer than 4 years was identified. The analysis of these patients and the search for possible reasons of the longer survival revealed several known favourable prognostic factors such as a longer disease-free survival of 5.5 years and a favourable pattern of metastasis, e.g., a prevalence of the locoregional and the skeletal type of metastasis. These two patterns comprised of 61% of the whole sample. In addition, however, a high frequency of concomitant diseases, most often disorders of metabolism, was observed among the cases. The leading diagnoses were type-2 diabetes mellitus and dyslipoproteinemias (Table I). Also, the number of a positive family history concerning breast cancer (25%) exceeded the expected value.

Diabetes mellitus. A prognostic favourable course of metastatic breast cancer in association with type-2 diabetes mellitus was described already in 1975 (8). The induction of tumor remissions in 7,12-dimethylbenz(a)anthracene

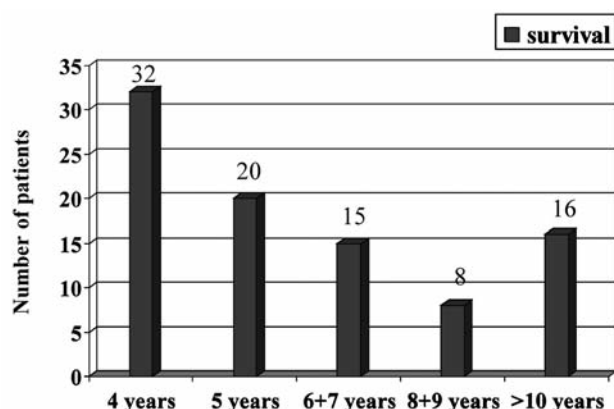


Figure 1. Distribution of survival times from the onset of unresectable recurrence and/or distant metastasis. Data from 91 patients with incurable breast cancer.

Table I. Coexistent diseases in 93 long-term survivors with metastatic breast cancer.

Concomitant disorders	N	Percentage
Diabetes mellitus type-2	41	44%
Hypercholesterinemia	22	24%
Other disorders of lipid metabolism	15	16%
Hyperuricemia / gout	11/3	12%
Endogenous psychosis	7	7.5%
Endocrine and other metabolic disorders	4	4%
Primary chronic polyarthritis	3	3%
Patients without the above disorders and without a family history of breast cancer	18	19%

(DMBA)-induced mammary carcinomas in rats by diazoxide, which causes a mild reversible diabetes, had supported the observation of a more favourable prognosis in breast cancer (9). Later, there was doubt about those clinical results since some authors reported that their patients with breast cancer and diabetes had a worse prognosis and developed metastases more frequently in comparison to patients without diabetes mellitus (10). These findings were clearly confirmed in recent years, when the questions around 'cancer and diabetes' received a renewed interest (11-13). Schrauder *et al.* found a 2-fold higher risk for distant metastases and an almost 2-fold increase in mortality compared to patients without diabetes mellitus (11), while the results of Kaplan *et al.* as well as Chen *et al.* suggested that diabetes is an independent predictor of lower breast cancer-specific and overall survival rates, even after adjusting for other comorbidities (12, 13). In the discussion about this contradiction, however, it was not taken into account that the description of a better prognosis was related to cases that had already developed metastatic

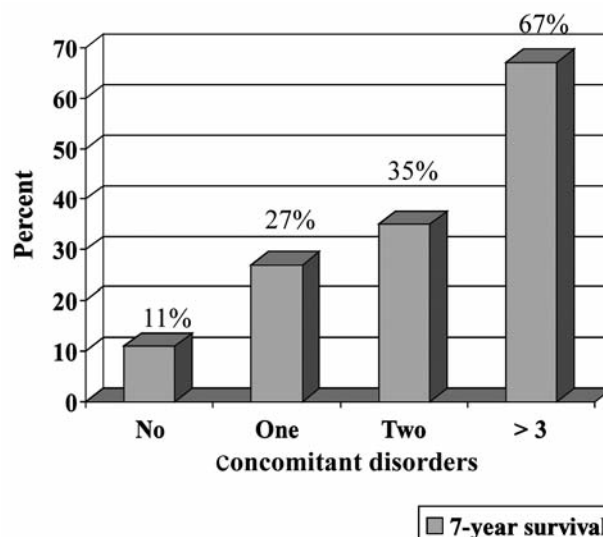


Figure 2. Rates of the 7-year survival related to concomitant disorders in patients with metastatic breast cancer.

disease (8), whereas Unterburger *et al.* (10) and other authors of recent publications (11-13) have analyzed the outcome of breast cancer populations from the time of diagnosis or primary surgery. Thus, to prevent misunderstandings, it seems of importance to distinguish between the prognosis of breast cancer patients with diabetes calculated from the time of diagnosis of the primary tumor or from the onset of an irresectable recurrence and/or metastasis, respectively.

The topic of diabetes mellitus and cancer found a broad interest during the last decade, which is reflected in an extensive literature; however, the influence of a diabetes (most often type 2) and its altered metabolism and insulin levels on tumor growth is an intriguing issue and some observations are seemingly contradictory. In general, insulin is regarded as a factor of promoting tumor growth. Hyperinsulinemia enhances *c-Myc*-mediated mammary tumor development and advances metastatic progression to the lung in a mouse model of type-2 diabetes. Furthermore, insulin-lowering therapy, using the beta-adrenergic receptor agonist CL-316243, reduced the metastatic burden in hyperinsulinemic mice to control levels (14). This would be in accordance with Goodwin *et al.* who noted that high levels of fasting insulin identify women with poor outcomes in early stage breast cancer (15) and similarly with the observations of several authors (10, 11) who described the rate of metastasis being twice as much in cases with breast cancer and diabetes compared to cases without a diabetes.

Fink *et al.* (16, 17) observed that increased insulin levels can enhance the effects of simultaneous cytotoxic treatment in a number of experimental systems. On the contrary,

Klenner *et al.* (18) have seen a loss of efficacy of cytotoxic chemotherapy with the addition of insulin in autochthonous mammary carcinomas of Sprague-Dawley rats. The whole issue around insulin, insulin-like growth factor (IGF) and breast cancer growth seems not settled yet (19), and since our diabetic patients have not further been analyzed with respect to plasma levels of insulin or IGF, the matter must be rather left aside. What about reports on the role of diabetes in other cancer forms? An exhaustive discussion of the extensive literature would go beyond the frame of this article but few examples may be of interest. Seemingly, paradox observations with regard to diabetes mellitus have been also made in colorectal carcinoma. On the one hand, type 2 diabetes seems to increase the risk of development of colorectal carcinoma in general (20) at the same time diabetes seems to lower the risk of developing distant metastasis (21). Furthermore, an inverse relationship between diabetes mellitus and the risk of developing prostate cancer has been reported; the exact underlying mechanisms of these observations remain unknown (22-24). In diabetic patients with hepatocellular carcinoma the prognosis was worse only in solitary tumors below a diameter of 3 cm. It was hypothesized that a reason for this could lie in a reduced tolerance of the hepatic tissue in diabetic patients, which might be overexposed to treatment measures since the tumors were small, allowing for repeated curative trials (25).

Meaning of concomitant diseases. If one considers the results of our study, the impression arising is that there exists a “law of a competition of two diseases”, whereby each condition may influence (or weaken) the clinical expression of the other. Examples for this phenomenon are frequently found in the literature. For instance, the majority of cases with familial medullary thyroid carcinoma are showing benign courses if they occur within the syndrome of multiple endocrine neoplasia (MEN) IIa (26). Other impressive mutual weakenings between two diseases are seen in patients with opso-myoclonus syndrome (OMS) and neuroblastoma. Patients with opso-myoclonus have a higher basic risk to develop neuroblastoma but in the course of the disease these patients have a remarkably good prognosis independent of their stage of disease or their age at diagnosis (27-30). The opso-clonus-myoclonus syndrome occurs in 2-3% of patients with neuroblastoma but neuroblastoma is found in as many as 50% of children who present with OMS. Nearly 100% of the children with neuroblastoma associated with OMS survive (29). A key role in the inhibition of tumor growth may be attributed to the expression of the oncogene *N-myc*. The degree of its amplification is an independent prognostic factor in neuroblastoma. In the case of OMS and neuroblastoma, single copies of *N-myc* seem to predominate, whereas patients with multicopy *N-myc* tumors have shown rapid tumor progression (27). Multifocal neuroblastomas

have also a more favourable prognosis. In a patient series of Hiyama *et al.*, all 8 tumors lacked *N-myc* gene (NMYC) amplification and expressed Ha-ras p21 protein (31). However, the *N-myc* mediated transcriptional repression in neuroblastoma is a complex process that is still not completely understood in our days (32).

A further example is the course of papillary thyroid cancer, which seems to be prolonged if the disease is associated with hypothyroidism due to Hashimoto’s thyroiditis (33) and, likewise, an improved survival in patients with head and neck cancer was seen when a hypothyroidism was diagnosed in addition (34). As in diabetes mellitus, a direct hormonal influence on tumor growth, rather than genetic mechanisms, may be assumed in these conditions.

Besides genetic or hormonal influences, non-cytotoxic drugs that are given for concomitant diseases could also cause tumor retardation. Examples may be anti-psychotics, with many of them having anti-tumor properties *in vitro* (35). Other drugs have been shown to alterate the lipid metabolism. Tamoxifen is able to decrease low density cholesterol and, as a rule, it increases the levels of triglycerides in a reversible manner (36-38). Metformin used in the treatment of diabetes mellitus seems to increase the rate of complete responses by neoadjuvant chemotherapy in early breast cancer (39). Drugs in common use with anti-metastatic activity in pre-clinical experiments, which, however, were clinically not fully examined in this respect, would be pentoxifylline, anti-coagulants, megestrol acetate and others (40).

Familial predisposition for breast cancer. A familial predisposition for breast cancer can be found in 15 to 20% of breast cancer patients and about 5% to 10% of all breast cancers are attributed to the breast cancer susceptibility genes *BRCA1* and *BRCA2* (41). The related research is accompanied by intriguing findings until today. Even the discovery of the cancer susceptibility genes *BRCA1/2* around the years 1994/1995 could not lead to unequivocal results concerning the prognosis. Many articles have been written and subgroups were defined, which had only a slightly aberrant course of the disease in comparison to sporadic breast cancer cases. The difficulties may arise from the fact that different biological features of a tumor can neutralize each other. For instance, medullary and poorly-differentiated carcinomas are more common in *BRCA1* mutation carriers. Despite this, the survival of these patients is not worse and the mutation might have out-weighted the unfavorable pathology features (42). To sum up, according to numerous earlier publications and newer reports, it can be said that the *BRCA* mutation status does not affect breast-cancer-related death rates in Western countries (43, 44).

Again, all this is true if one keeps in mind that these investigations were based on prospective studies defining breast cancer’s course from the diagnosis of the primary

tumor. The influence of genetic mutations, with regard to a familial predisposition on the course of the segment of breast cancers with proven metastasis, has not been prospectively investigated. Such an influence has yet to be postulated.

It was shown that *BRCA*-mutations were also associated with a significantly prolonged survival in ovarian carcinoma in a large study from Israel (45). Similar relations were reported for colorectal cancer. If colorectal cancer is associated with hereditary breast cancer, the colon tumors appear earlier in life and have a lower tumor stage and a better survival rate than the general population (46).

Is there a common genetic denominator? A common genetic denominator of the conditions associated with a longer survival in metastatic breast cancer patients is not visible. First of all, the favourable prognostic factors, such as the long disease-free interval or the pattern of metastasis, can presently not be linked to certain genetic alterations. There seems to exist a rather unspecific genetic/epigenetic imbalance expressing itself in various concomitant diseases. Also a family history for breast cancer probably means a genetic alteration even we do not know all of its details. It remains unknown how genetic alterations, which are not obviously related to tumor suppressor genes, interact with inhibitors of tumour growth. Many possible genetic pathways for a tumor suppression appear on the horizon if one considers only the Down syndrome (47), as it seems that – at least in the field of colorectal cancer genomics – there is evidence for multiple genotypes influencing survival supporting the paradigm “the more genetic aberrations, the better the survival” (48).

Therefore, concomitant diseases may influence the slow-down of tumor growth in different ways, for instance, through immediate effects on tumor growth *via* hormones or genetically by gene silencing *via* methylation of promoters regulating gene activity or other mechanisms, and possibly by non-cytotoxic drugs that are given for concomitant diseases.

Conflicts of Interest

The Authors declare that there are no conflicts of interest concerning this manuscript.

References

- Clark GM, Sledge GW, Osborne CK and McGuire WL: Survival from first recurrence: Relative importance of prognostic factors in 1015 breast cancer patients. *J Clin Oncol* 5: 55-61, 1987.
- Cold S, Jensen NV, Brincker H and Rose C: The influence of chemotherapy on survival after recurrence in breast cancer: a population based study of patients treated in the 1950s, 1960s, and 1970s. *Eur J Cancer* 29A(8): 1146-1152, 1993.
- Bergh J, Jönsson PE, Glimelius P and Nygren P (SBU-group. Swedish Council of Technology Assessment in Health Care): A systematic overview of chemotherapy effects in breast cancer. *Acta Oncol* 40: 253-281, 2001.
- Legha SS and Blumenschein GR: Systemic therapy of metastatic breast cancer: A review of the current trends. *Oncology* 39: 140-145, 1982.
- Khodadad K, Sturtz F, Pujade-Lauraine E and Belpomme D: Over 25% 5-year-overall survival in patients with metastatic breast carcinoma receiving the VVF protocol in addition to conventional treatments. *Procc ASCO* 20: 49b (#1943), 2001.
- Possinger K, Schmid P, Schmoll HJ, Höffken K, Kreienberg R and Dunst J: Breast Cancer. *In: Kompendium Internistische Onkologie* (Schmoll HJ, Höffken K, Possinger K (eds.). Heidelberg, Springer, pp. 4215-4331, 2006.
- Falkson G, Holcroft C, Gelman, Tormey DC, Wolter JM and Cummings FJ: Ten-year follow-up study of premenopausal women with metastatic breast cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 13: 1453-1458, 1995.
- Rhombert W: Metastasizing carcinoma of the breast and diabetes mellitus, a prognostically favourable combination. *Dt Med Wschr* 100: 2422-2427, 1975.
- Berger MR, Fink M, Feichter GE and Janetschek P: Effects of Diazoxide-induced reversible diabetes on chemically induced autochthonous mammary carcinomas in Sprague-Dawley rats. *Int J Cancer* 35: 395-401, 1985.
- Unterburger P, Sinop A, Noder W, Berger MR, Fink M, Edler L, Schmähl D and Ehrhart H: Diabetes mellitus und Mammakarzinom. Eine retrospektive Verlaufsstudie. *Onkologie* 13: 17-20, 1990.
- Schrauder MG, Fasching PA, Häberle L, Lux MP, Rauh C, Hein A, Bayer CM, Heusinger K, Hartmann A, Strehl JD, Wachter DL, Schulz-Wendtland R, Adamietz B, Beckmann MW and Loehberg CR: Diabetes and prognosis in a breast cancer cohort. *J Cancer Res Clin Oncol* 137: 975-983, 2011.
- Kaplan MA, Pekkolay Z, Kucukoner M, Inal A, Urakci Z, Ertugrul H, Akdogan R, Firat U, Yildiz I and Isikdogan A: Type 2 diabetes mellitus and prognosis in early stage breast cancer women. *Med Oncol* 29(3): 1576-1580, 2012.
- Chen WW, Shao YY, Shau WY, Lin ZZ, Lu YS, Chen HM, Kuo RN, Cheng AL and Lai MS: The impact of diabetes mellitus on prognosis of early breast cancer in Asia. *Oncologist* 17: 485-491, 2012.
- Ferguson RD, Novosyadlyy R, Fierz Y, Alikhani N, Sun H, Yakar S and Leroith D: Hyperinsulinemia enhances c-Myc-mediated mammary tumor development and advances metastatic progression to the lung in a mouse model of type 2 diabetes. *Breast Cancer Res* 14(1): R8, 2012.
- Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, Hartwick W, Hoffman B and Hood N: Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. *J Clin Oncol* 20: 42-51, 2002.
- Fink M, Abenhardt W, Ostermayr B and Berger M: Insulin and Diazoxide for treatment of cancer. *Onkologie* 14: 158-164, 1991.
- Fink M: Insulin as growth factor for malignancies (editorial). *Muench Med Wschr* 133: 69, 1991.
- Klenner T, Berger MR, Zelezny O, Fink M and Schmähl D: Antineoplastic efficacy of melphalan and N-(2-chloroethyl)-N-nitrosocarbamoyl-lysine, in combination with diazoxide or insulin in autochthonous mammary carcinoma of the Sprague-Dawley rat. *J Cancer Res Clin Oncol* 116: 45-50, 1990.
- Surmacz E, Guvakova MA, Nolan MK, Nicosia RF and Sciacca L: Type I insulin-like growth factor receptor function in breast cancer. *Breast Cancer Res Treat* 47: 255-267, 1998.

- 20 Nagel JM and Göke B: Colorectal carcinoma screening in patients with type 2 diabetes mellitus. *Z Gastroenterol* 44: 1153-1165, 2006.
- 21 Nagel JM, Bücker S, Wood M, Stark R, Göke B, Parhofer KG and Allgayer H: Less advanced stages of colon cancer in patients with type 2 diabetes mellitus: an unexpected finding? *Exp Clin Endocrinol Diabetes* 120: 224-228, 2012.
- 22 Bonovas S, Filioussi K and Tsantes A: Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 47(6): 1071-1078, 2004.
- 23 Kasper JS, Liu Y and Giovannucci E: Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. *Int J Cancer* 124(6): 1398-1403, 2009.
- 24 Kasper JS and Giovannucci E: A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15: 2056-2062, 2006.
- 25 Toyoda H, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriya S, Tanikawa M, Sone Y and Hisanaga Y: Impact of diabetes mellitus on the prognosis of patients with hepatocellular carcinoma. *Cancer* 91: 957-963, 2001.
- 26 Emmertsen K, Elbrond O, Nielsen HE, Mosekilde L, Charles P, Kaae S and Hansen HH: Familial medullary thyroid carcinoma in multiple endocrine neoplasia (MEN) IIa: Diagnosis and problems in treatment. *Eur J Cancer Clin Oncol* 18: 645-650, 1982.
- 27 Cohn SL, Salwen H, Herst CV, Maurer HS, Nieder ML, Morgan ER and Rosen ST: Single copies of the N-myc oncogene in neuroblastomas from children presenting with the syndrome of opsoclonus-myoclonus. *Cancer* 62(4): 723-726, 1988.
- 28 Altman AJ and Baehner RL: Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. *Cancer* 37: 846-852, 1976.
- 29 Rothenberg AB, Berdon WE, D'Angio GJ, Yamashiro DJ and Cowles RA: The association between neuroblastoma and opsoclonus-myoclonus syndrome: a historical review. *Pediatr Radiol* 39: 723-726, 2009.
- 30 Warriar RP, Kini R, Besser A, Wiatrok B and Raju U: Opsomyoclonus and neuro- blastoma. *Clin Pediatr (Phila)* 24(1): 32-34, 1985.
- 31 Hiyama E, Yokoyama T, Hiyama K, Yamaoka H, Matsuura Y, Nishimura Si and Ueda K: Multifocal neuroblastoma. Biologic behavior and surgical aspects. *Cancer* 88: 1955-1963, 2000.
- 32 Gherardi S, Valli E, Erriquez D and Perini G: MYCN-mediated transcriptional repression in neuroblastoma: the other side of the coin. *Front Oncol* 2013; doi: 10.3389/fonc.2013.00042
- 33 Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A and Shah JP: Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. *Surgery* 126: 1070-1076, 1999.
- 34 Nelson M, Hercbergs A, Rybicki L and Strome M: Association between development of hypothyroidism and improved survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 132: 1041-1046, 2006.
- 35 Carrillo JA and Benítez J: Are antipsychotic drugs potentially chemopreventive agents for cancer? *Eur J Clin Pharmacol* 55(6): 487-488, 1999.
- 36 Brun DL, Gagne C, Rousseau C, Moorjani S and Lupien PJ : Severe lipemia induced by tamoxifen. *Cancer* 57: 2123-2126, 1986.
- 37 Cuzick J, Allen D, Baum M, Barrett J, Clark G, Kakkar V, Melissari E, Moniz E, Moore J and Parsons V: Long term effects of tamoxifen. Biological effects of Tamoxifen Working Party. *Eur J Cancer* 29A(1): 15-21, 1992.
- 38 Love RR, Newcomb PA, Wiebe DA, Surawicz TS, Jordan VC, Carbone PP and DeMets DL: Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. *J Natl Cancer Inst* 82: 1327-1332, 1990.
- 39 Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, Hsu L, Hung MC, Hortobagyi GN and Gonzalez-Angulo AM: Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 27: 3297-3302, 2009.
- 40 Rhomberg W: Antimetastatic Treatment Approaches in the Clinic: Previous and Present Evidence. In: *Horizons in Cancer Research* (Watanabe HS, Ed). Vol 46:1-21(Chapter IV), Nova Science Publishers, Inc., 2011. ISBN 978-1-61209-922-4.
- 41 Jacobi CE, Jonker MA, Nagelkerke NJD, van Houwelingen JC and de Bock GH: Prevalence of family histories of breast cancer in the general population and the incidence of related seeking of health care. *J Med Genet* 40: e83, 2003. doi: 10.1136/jmg.40.7.e83.
- 42 Lynch HT and Watson P: BRCA1, Pathology, and Survival (Editorial). *J Clin Oncol* 16: 395-396, 1998.
- 43 Rennert G, Bisland-Naggan S, Barnett-Griness O, Bar-Joseph N, Zhang S, Rennert HS and Narod SA: Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. *N Engl J Med* 357: 115-123, 2007.
- 44 Goodwin PJ, Phillips KA, West DW, Ennis M, Hopper JL, John EM, O'Malley FP, Milne RL, Andrulis IL, Friedlander ML, Southey MC, Apicella C, Giles GG and Longacre TA: Breast cancer prognosis in BRCA1 and BRCA2 mutation carriers: an International Prospective Breast Cancer Family Registry population based cohort study. *J Clin Oncol* 30(1): 19-26, 2012.
- 45 Ben David Y, Chetrit A, Hirsh-Yechezkel G, Friedman E, Beck BD, Beller U, Ben-Baruch G, Fishman A, Levavi H, Lubin F, Menczer J, Piura B, Struwing JP and Modan B; National Israeli Study of Ovarian Cancer: Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. *J Clin Oncol* 20: 463-466, 2002.
- 46 Lin KM, Ternent CA, Adams DR, Thorson AG, Blatchford GJ, Christensen MA, Watson B and Lynch HT: Colorectal cancer in hereditary breast cancer kindreds. *Dis Colon Rectum* 42: 1041-1045, 1999.
- 47 Threadgill DW: Down's syndrome. Paradox of a tumor repressor. *Nature* 451: 21-22, 2008.
- 48 Rooney PH, Boonsong A, McKay JA, Marsh S, Stevenson DAJ, Murray GI, Curran S, Haites NE, Cassidy J and McLeod HL: Colorectal cancer genomics: evidence for multiple genotypes which influence survival. *Br J Cancer* 85(10): 1492-1498, 2001.

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