Multiple Susceptibility Loci for Radiation-Induced Mammary Tumorigenesis in F2[Dahl S x R]-Intercross Rats

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Abstract

Although two major breast cancer susceptibility genes, BRCA1 and BRCA2, have been identified accounting for 20% of breast cancer genetic risk, identification of other susceptibility genes accounting for 80% risk remains a challenge due to the complex, multi-factorial nature of breast cancer. Complexity derives from multiple genetic determinants, permutations of gene-environment interactions, along with presumptive low-penetration of breast cancer predisposing genes, and genetic heterogeneity of human populations. As with other complex diseases, dissection of genetic determinants in animal models provides key insight since genetic heterogeneity and environmental factors can be experimentally controlled, thus facilitating the detection of quantitative trait loci (QTL). We therefore, performed the first genome-wide scan for loci contributing to radiation-induced mammary tumorigenesis in female F2-(Dahl S x R)-intercross rats. Tumorigenesis was measured as tumor burden index (TBI) after induction of rat mammary tumors at forty days of age via 127Cs-radiation. We observed a spectrum of tumor latency, size-progression, and pathology from poorly differentiated ductal adenocarcinoma to fibroadenoma, indicating major effects of gene-environment interactions. We identified two mammary tumorigenesis susceptibility quantitative trait loci (Mts-QTLs) with significant linkage: Mts-1 on chromosome-9 (LOD-2.98) and Mts-2 on chromosome-1 (LOD-2.61), as well as two Mts-QTLs with suggestive linkage: Mts-3 on chromosome-5 (LOD-1.93) and Mts-4 on chromosome-18 (LOD-1.54). Interestingly, Chr9-Mts-1, Chr5-Mts-3 and Chr18-Mts-4 QTLs are unique to irradiation-induced mammary tumorigenesis, while Chr1-Mts-2 QTL overlaps with a mammary cancer susceptibility QTL (Mcs-3) reported for 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis in F2[COP x Wistar-Furth]-intercross rats. Altogether, our results suggest at least three distinct susceptibility QTLs for irradiation-induced mammary tumorigenesis not detected in genetic studies of chemically-induced and hormone-induced mammary tumorigenesis. While more study is needed to identify the specific Mts-gene variants, elucidation of specific variant(s) could establish causal gene pathways involved in mammary tumorigenesis in humans, and hence novel pathways for therapy.

Introduction

Breast cancer is one of the most prevalent female cancers in the world, affecting at least 10% of women in industrialized nations [1,2]. Breast cancer is a complex multifactorial trait encompassing genetic and environmental factors [3,4]. To date few breast cancer susceptibility genes have been identified in human populations with BRCA1 and BRCA2 variants accounting for less than 20% of the genetic risk of breast cancer [5]. Due to the complex inheritance of this disorder and genetic heterogeneous nature of human populations it has been difficult to unravel novel breast cancer susceptibility/resistance genes that could elucidate novel pathways for diagnosis, treatment and prevention of breast cancer.

Two classes of rat models of mammary carcinogenesis have been frequently used; chemically-induced mammary carcinogenesis using compounds like the polycyclic aromatic hydrocarbon 7,12-dimethylbenz[a]anthracene (DMBA) [6], N-nitroso-N-methylurea (NMU) [7], 2-amino-1-methyl-6phenylimidazo[4,5-b]pyridine (PhIP) [8], estrogens [9] and radiation-induced mammary carcinogenesis [10–15]. Of the few reported genetic studies that have been performed in animal models of mammary carcinogenesis, all have utilized the chemically-induced model as the chosen animal model system [3]. Thus, QTLs affecting susceptibility to mammary tumors have been reported in rat intercrosses subjected to DMBA-induced [16] and 17β-Estradiol-induced [17] mammary carcinogenesis. However, there are no reports on genetic studies performed on radiation-induced mammary carcinogenesis, despite the fact that ionizing radiation is one of the few well-characterized etiologic factors of human breast cancer [18] and the well-established fact that the female breast is one of the most susceptible organs to radiation-induced cancer [19–22].

The objective of this study was to perform a genome scan for QTLs affecting radiation-induced tumorigenesis. The sample used was an F2 (Dahl S x R)-intercross female rat population phenotyped for radiation-induced mammary tumorigenesis after induction of rat mammary gland tumors at 40 days of age via 127Cs-radiation. We chose the Dahl S/Dahl R rat model because these two inbred rat lines were derived from the Sprague-Dawley...
Results

In order to assess potential differences in susceptibility to radiation-induced tumorigenesis we first analyzed inbred parental strains, Dahl S and Dahl R female rats, selected for the observed tendency to develop spontaneous mammary tumors in F2 [Dahl S x R]-intercross rats. We measured latency to tumor development and number of mammary gland tumors after a single dose of irradiation at 40 days of age in parental Dahl S and Dahl R female rats. As shown in Figure 1, Dahl R rats exhibited decreased tumor latency and increased tumor burden index compared with Dahl S rats (P<0.05), indicating increased radiation-induced breast cancer susceptibility in Dahl R female rats.

We next performed a total genome scan for QTLs affecting radiation-induced mammary tumorigenesis susceptibility (Mts) using 150 F2 (Dahl S x R)-intercross female rats phenotyped for tumor burden index (TBI) as the quantitative measure for tumorigenicity measuring both latency to tumor formation and number of tumors. We detected two Mts-QTLs with significant linkage: Mts-1 on chromosome 9, LOD 2.98 and Mts-2 on chromosome 1, LOD 2.61; Table 1 and Figure 2). We also detected two Mts-QTLs with suggestive linkage (Mts-3 on chromosome 5, LOD 1.93 and Mts-4 on chromosome 18, LOD 1.54; Table 1 and Figure 2). Additional analysis for interactive effects on breast cancer susceptibility reveals no gene-gene interaction in this F2 (Dahl S x R)-intercross female rat cohort. Histopathological analysis of representative Hematoxylin and Eosin stained sections from seven rats detected mammary adenocarcinomas in five, including poorly differentiated adenocarcinoma (Figure 3), and fibroadenomas in two (Figure 3). This is typical of syntenic regions to Mts-1 to Mts-4 in humans reveals candidate genes previously implicated in breast cancer. On chromosome 9, Poph (prolactin releasing hormone) is a candidate gene for Mts-1 QTL. Since Poph maps to rat chromosome-9 at coordinate 90.15 Mbp within the Mts-1 QTL region (Table 1). Poph modulates secretion of prolactin [28], a hormone that has been shown to be a risk factor for human breast cancer [28,29]. Notably, for Mts-2 QTLs on chromosome-1, the marker at the QTL-peak, D1Rat350, is located within the Aooap [alanine (membrane) aminopeptidase] transcription unit, an enzyme that might be a candidate gene because it has been associated with invasive colorectal cancer [30] and prostate cancer [31], and Barrett's adenocarcinoma [32]. Another candidate gene on chromosome 1, Bin localizes at 136.2 Mb also within the Mts-2 QTL interval (Table 1). Notably, Bin [Bloom syndrome homolog] has been implicated in breast cancer susceptibility in humans [33,34]. The Mts-3 chromosome-5 QTL region (Table 1) harbors Ecel (endothelin-converting enzyme-1 at 156.6 Mb), an enzyme that has also been implicated in human breast cancer [35,36]. Finally, within the Mts-4 interval on chromosome 18 (Table 1) resides Smad2 (SMAD family member 2/mothers against decapentaplegic homolog 2, 73.18 Mb), a signaling protein whose phosphorylation mediates TGF-beta induced breast cancer invasiveness [37,38].

Discussion

This is the first genome-wide scan for QTLs affecting radiation-induced mammary tumorigenesis in rodents. We detected two significant Mts-QTLs on chromosomes 9 and 1 and two suggestive Mts-QTLs on chromosomes 5 and 18. The chromosome 9 Mts-1, chromosome 5 -Mts-3 and chromosome 18 Mts-4 QTLs represent novel QTL regions associated with mammary tumorigenesis not previously observed in other rat intercrosses of DMBA-induced and estrogen-induced mammary tumorigenesis [3]. Mts-2 QTL spanning chromosome 125–145 Mbp region overlaps with Mts3 QTL that maps to chromosome 109.1–138.8 Mbp region in a COP x WF intercross rat population phenotyped for DMBA-induced mammary carcinogenesis [16]. Interestingly, both QTLs decrease susceptibility to tumorigenesis suggesting that the same gene might underlie both QTLs effects on mammary tumorigenesis. Mts-3 mapping to chromosome 5 147–167 Mbp region partially overlaps with Emc1 spanning chromosome 5 107–159 Mbp region detected in an F2 (COP x ACI)-intercross rat population characterized for estrogen-induced mammary carcinogenesis [39]. However, having different modes of inheritance, recessive for Emc1 and co-dominant or additive for Mts-3, data suggest that different genes might account for these two QTL effects on rat mammary tumorigenesis. Finally, Mts-4 at chromosome 18 66–86 Mbp region partially overlaps with Msta2 that peaks at 68 Mbp in a SPRD-Cu3 x WKY backcross rat population characterized for DMBA-induced mammary carcinogenesis [40]. However, Mts-4 and Msta have opposite effects on susceptibility with Msta decreasing and Mts-4 increasing susceptibility to mammary tumorigenesis suggesting that different genetic determinants underlie these QTLs effects on tumorigenesis. Altogether, the data suggest that distinct genetic determinants exist that confer susceptibility to irradiation-induced mammary tumorigenesis from those loci affecting chemically-induced and estrogen-induced mammary tumorigenesis.

As described by Cronkite et al 1960 [27], radiation-induced mammary tumor models exhibits both adenocarcinoma and fibroadenoma in Sprague Dawley rats. Notably, both adenocarcinoma and fibroadenoma were also detected in the F2[Dahl S x
R]) breast cancer cohort studied here concordant with the fact that both Dahl S and Dahl R rats were derived from Sprague Dawley rats selected for salt-sensitive and salt-resistant hypertension respectively. Given the same environmental insult, the spectrum of pathologies from malignant to benign, and the detection of multiple QTLs suggest that susceptibility to mammary tumorigenesis is a complex multifactorial event likely involving multiple genetic determinants and genetic modifiers. As spectrum of susceptibility, the data suggest that genetic analysis for sporadic breast cancer and fibroadenoma can be analyzed as one pathogenic event with a spectrum much like other diseases.

Although further studies are needed to identify causal genes in respective Mts-QTLs, the panel of candidate genes with reported gene expression changes or polymorphisms in breast cancer patients, Prlh for Mts-1, Anppg or Blm for Mts-2, Ece1 for Mts-3, and Smad2 for Mts-4 validate the hypotheses that these genes should be studied further in different experimental systems and in humans as potential susceptibility genes for mammary tumorigenesis. Although no statistically significant genetic interaction was detected among the QTLs, we note all Mts-QTLs 1–4 candidate genes are associated with key aspects of breast tumor progression and malignancy, which collectively could increase tumorigenesis susceptibility. Increased Prlh leading to higher prolactin levels is associated with increased risk for breast cancer, increased metastasis, disease progression, lower response to tamoxifen and worse clinical prognosis [41]. Furthermore, Prlh as a candidate gene for Mts-1 QTL is concordant with the observation that prolactin accelerated mammary tumorigenesis initiated by radia-

Figure 2. QTLs for mammary tumorigenesis susceptibility (Mts) in F2 [Dahl S x R]-intercross female rats. Chromosomes with significant and suggestive QTLs were analyzed by interval mapping with bootstrap resampling method to estimate a confidence interval (QTXb19 Map Manager): Panel A, chromosome 9 (Mts-1); B, chromosome 1 (Mts-2); C, chromosome 5 (Mts-3); D, chromosome 18 (Mts-4). Yellow histograms represent the bootstrap-based confidence intervals for the detected QTLs. Orientation of chromosomes: left → right starting from lowest Mbp. Horizontal green lines mark LOD values for significance of linkage, from top to bottom: significant LOD ≥ 2.48; suggestive LOD ≥ 1.30; LOD (black line); regression coefficient for additive effect (red line).

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tion [42]. Similarly, the candidate genes for Mts-2 QTL, Anpep or Blm are both implicated in breast cancer. Anpep is increased in breast cancer effusions [43], and its down regulation is associated with invasive colorectal cancer [30] and prostate cancer [31], while over expression of Anpep has been linked to Barrett’s adenocarcinomas [32]. Blm, the gene for Bloom syndrome, is a DNA repair gene which may play a role in breast cancer occurrence as its loss may contribute to somatic mutations and loss of heterozygosis, chromosomal instability, aneuploidy, and sensitivity to DNA damaging agents [44]. For Mts-3 QTL candidate gene, Ece1, cumulative studies point to its role in breast cancer invasiveness and more frequent recurrence [45]. Lastly, Mts-4 QTL candidate gene, Smad2, underlies Smad2-dependent epithelial mesenchymal transition of breast cancer cells [46], a key step in invasiveness and subsequent metastasis. Intriguingly, the deduced synergisms from these breast cancer roles for each Mts QTL candidate gene suggest the hypothesis that QTL-burden could increase risk, reiterating the need for further study.

Further inspection of the Rat Genome Database (RGD) reveals additional candidate genes within Mts-1, Mts-2, Mts-3 and Mts-4 QTL regions. These candidate genes include the DNA repair gene Blm, as well as genes involved in cell motility and invasion, such as Ece1 and Smad2. The cumulative evidence suggests that these genes may play a role in breast cancer occurrence and progression.

Figure 3. Hematoxylin and Eosin stained digital photomicrographs of representative breast tumor phenotypes in the F2-cohort of radiation-induced breast tumors. A, Adenoductal carcinoma phenotype, B, fibroadenoma. →, representative duct morphology in each section; *, hyaline (pink) fibrous tissue markedly increased in fibroadenoma.

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4 QTLs that have been associated with different types of cancers (Table 2). However, more studies involving fine mapping through sub-strain construction will be necessary to identify the genes underlying these QTLs.

Table 1. QTLs for mammmary tumorigenesis susceptibility in F2 (Dahl S x R)-intercross female rats.

| QTL | Location | LOD | % | QTL* | Candidate
|---|---|---|---|---|---
| Mts-1 | Chr9:94–104 Mbp | 2.98 (S) | 9 (↓) | Prlh |
| Mts-2 | Chr1:125–145 Mbp | 2.61 (S) | 8 (↓) | Mts3 [16] | Anpep or Blm |
| Mts-3 | Chr5:147–167 Mbp | 1.93 (Sug) | 6 (↑) | Ece1 |
| Mts-4 | Chr18:66–86 Mbp | 1.54 (Sug) | 5 (↑) | Smad2 |

Table 2. Genes associated with cancer within mammmary tumorigenesis susceptibility QTLs detected in F2 (Dahl S x R)-intercross female rats.

| Symbol | Description | Location (nt) | Association [ref]
|---|---|---|---
| Mts-1 (Chr9) | Ugt1a7c | UDP glucuronosyltransferase 1 family, polypeptide A7C | 87029500–87098362 | Pancreatic cancer [47] |
| Mts-1 (Chr9) | Ugt1a1 | UDP glucuronosyltransferase 1 family, polypeptide A1 | 87091241–87098362 | Endometrial cancer [48], ovarian cancer [49] |
| Mts-1 (Chr9) | Pam | Peptidylglycine alpha-amidating monooxygenase | 96893071–97047523 | Prostate cancer [50] |
| Mts-2 (Chr1) | Ralbp1 | RalA binding protein 1 | 104617400–104653856 | Bladder cancer [51] |
| Mts-3 (Chr5) | Ntrk3 | Neurotrophic tyrosine kinase, receptor, type 3 | 133925530–134302139 | Prostate cancer [52] |
| Mts-3 (Chr5) | Fzd4 | Frizzled family receptor 4 | 145953743–145957666 | Prostate cancer [53] |
| Mts-4 (Chr18) | Hdac1 | Histone deacetylase 1 | 148672515–148699810 | Breast cancer [54], cervical cancer [55], endometrial cancer [56], ovarian cancer [56] |
| Mts-4 (Chr18) | Sfn | Stratifin | 151475395–151479996 | Breast cancer [57], endometrial cancer [58], prostate cancer [57] |
| Mts-4 (Chr18) | Runx3 | Runt-related transcription factor 3 | 153950116–153973141 | Breast cancer [59], ovarian cancer [60], colorectal cancer [61] |
| Mts-4 (Chr18) | Wnt4 | Wingless-type MMTV integration site family, member 4 | 156064371–156083198 | Endometrial cancer [62] |
| Mts-4 (Chr18) | Sdhb | Succinate dehydrogenase complex, subunit B, iron sulfur[8] | 159818669–159839772 | Renal cancer [63] |
| Mts-4 (Chr18) | Casp9 | Caspase 9, apoptosis-related cysteine peptidase | 160704234–160721796 | Breast cancer [64] |
| Mts-4 (Chr18) | Tnfrf1b | Tumor necrosis factor receptor superfamily, member 1b | 163666541–163697484 | Renal cancer [65] |
| Mts-4 (Chr18) | Smad4 | SMAD family member 4 | 7042705–70461541 | Ovarian cancer [66], endometrial cancer [67] |
| Mts-4 (Chr18) | Smad7 | SMAD family member 7 | 72294803–72323354 | Endometrial cancer [68] |

Table legend: Genes and gene locations on rat chromosomes 1, 5, 9 and 18 regions as per RGD. nt, nucleotide; ref, reference.
protocol was approved by the Committee on the Ethics of Animal Experiments of Boston University School of Medicine (Permit Number: AN-13924).

Genetic Crosses

Dahl S/jrHsd and Dahl R/jrHsd rats were obtained from Harlan (Indianapolis, Indiana). Parental strains (Dahl R/jrHsd female × Dahl S/jrHsd male) were crossed to produce F1 progeny. The F2 subjects were derived from brother-to-sister mating of F1 hybrids to produce the F2 female (n = 150) segregating population.

Phenotypic Characterization and Genotyping

Animals were maintained on a LabDiet 5001 rodent chow (Harlan Teklad, Madison WI) containing 0.23% NaCl. We induced rat mammary gland tumors in 12 Dahl S/jrHsd, 12 Dahl R/jrHsd and 150 F2 female subjects as described [27] at 40 days of age via 127Cs-radiation. Rats were exposed to 400 r of whole body radiation. All subjects were sacrificed when tumor burden reached a total of 3 cm in diameter for animals harboring one or multiple tumors or at 12 months of age for those that did not develop tumors. Three out of 12 Dahl S/jrHsd, seven out 12 Dahl R/jrHsd and ninety eight out of 150 F2 female rats developed mammary tumors. Seven F2 female rat tumors were randomly selected for histological analysis (five were found to be carcinomas and two were fibroadenomas). Routine Hematoxylin and Eosin stained histological sections were obtained from 4% paraformaldehyde fixed tissue samples and analyzed with a clinical tumor pathologist [Michael J O’Brien, MD, MPH] at Boston Medical Center. Tumor latency was computed from 40 days of age (at time of radiation). Tumor latency was computed from 40 days of age (at time of radiation). Tumor burden index was computed using the formula TBI = 1+[Tx2]+[TLAT/TL] (T = # tumors; TLAT = highest tumor latency; TL = tumor latency) as described [69]. Linkage maps, marker regression and composite interval mapping were done with the Map Manager QTXb19 (MMQTXb19) program for windows [70] which generates a likelihood ratio statistic (LRS) as a measure of the significance of a possible QTL. Genetic distances were calculated using Kosambi mapping function (genetic distances are expressed in centiMorgan, cM). Critical significance values (LRS values) for interval mapping were determined by a permutation test (2000 permutations at all loci tested) on our female cohort using Kosambi mapping function and an additive regression model. Values for suggestive linkage LRS = 6.0 (LOD 1.30) and for significant linkage LRS = 11.4 (LOD 2.48). LRS 4.6 delineates LOD 1-support interval. Confidence interval for a QTL location was estimated by bootstrap resampling method wherein histogram single peak delineates the QTL and peak widths define confidence interval for the QTL. Histograms which show more than one peak warn that the position for the QTL is not well defined or that there may be multiple linked QTLs (QTX Map Manager). We also performed interaction analysis using the Map Manager QTXb19 program applying a two-stage test paradigm for determination of interaction in which the pair of loci must pass two tests in order to be reported as having a significant interaction effect. First, the significance of the total effect of the two loci must be <0.00001 and second, the pairs of loci must exhibit a P value <0.01 for the interaction effect.

Author Contributions

Conceived and designed the experiments: NRO. Performed the experiments: VLH LRP. Analyzed the data: VLH NRO. Wrote the paper: VLH NRO.

References

1. Bray F, McCarron P, Parkin DM (2004) The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 6: 229–239.
2. Parkin DM (2001) Global cancer statistics in the year 2000. Lancet Oncol 2: 533–543.
3. Shull JD (2007) Mammary cancer susceptibility: human genes and rodent models. Mamm Genome 18: 817–831.
4. Easton DF (1999) How many more breast cancer predisposition genes are there? Breast Cancer Res 1: 14–17.
5. Huggins C, Grand LC, Brillantes FP (1961) Mammary cancer induced by a single feeding of polynuclear hydrocarbons, and its suppression. Nature 189: 204–207.
6. Vollnoh PM, Pettigrew HM, Grantham FH (1973) N-Nitrosomethylurea as a mammary cancer carcinogen in rats. J Natl Cancer Inst 54: 401–414.
7. Ito N, Hasegawa R, Sano M, Tamano S, Esumi H, et al., (1991) A new colon and mammary cancer carcinogen in cooked food, 2-amino-1-methyl-6-phenylimino-4,3-biphenylidine (PhIP). Carcinogenesis 12: 1503–1506.
8. Harvell DM, Streecker TE, Xie B, Buckles LK, Tochacek M, et al., (2007) Genetic interaction in estrogen-induced mammary carcinogenesis in the ACI rat. J Nutrition 131: 3087S–3091S.
9. Gragtmans NJ, Myers DK, Johnson JR, Jones AR, Johnson LD (1984) Occurrence of mammary tumors in rats after exposure to tritium beta rays and 14.8 MeV neutrons and steroid receptor content of these tumor types. Cancer Lett 6: 147–153.
10. Gragtmans NJ, Myers DK, Johnson JR, Jones AR, Johnson LD (1984) Occurrence of mammary tumors in rats after exposure to tritium beta rays and 14.8 MeV neutrons and steroid receptor content of these tumor types. Cancer Lett 6: 147–153.
11. Lepsoy HM, Kumar PF, Peterson C, Rodriguez-Sierra JF, Abbo KM (1989) Inhibition of radiographic mammary carcinoma in rats by estradiol or tamoxifen. Cancer 63: 1685–1692.
12. Mandelbrot T, Ormsby I, Samuels S, Mancardi GL (1985) Neural, pituitary and mammary tumors in Sprague-Dawley rats treated with X irradiation to the head and N-ethyl-N-nitrosourea (ENU) during the early postnatal period: a statistical study of tumor incidence and survival. Radiat Res 101: 460–472.
13. Shellabarger CJ, Cronkite EP, Bond VP, Lippincott SW (1957) The occurrence of mammary tumors in the rat after sublethal whole-body irradiation. Radiat Res 6: 501–512.
14. Welsch CW, Goodrich-Smith M, Brown CK, Migliore N, Collin KH (1981) Effect of an estrogen antagonist (tamofoxifen) on the initiation and progression of gamma-irradiation-induced mammary tumors in female Sprague-Dawley rats. Eur J Cancer Clin Oncol 17: 1253–1258.
15. Shepel LA, Lan H, Haag JD, Brasic GM, Ghen ME, et al., (1996) Genetic identification of multiple loci that control breast cancer susceptibility in the rat. Genetics 149: 289–299.
16. Schaffer BS, Lachel CM, Pennington KL, Murrin CR, Streecker TE, et al., (2006) Genetic bases of estrogen-induced tumorigenesis in the rat: mapping of loci controlling susceptibility to mammary cancer in a Brown Norway x ACI intercross. Cancer Res 66: 7793–7800.
17. Smith-Bindman R (2012) Environmental causes of breast cancer and radiation from medical imaging: findings from the Institute of Medicine report. Arch Intern Med 172: 1023–1027.
18. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, et al., (2002) Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 168: 197–200.
19. Preston DL, Ross E, Tokuda S, Funamoto S, Nishij N, et al., (2007) Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 168: 1–64.
24. Imaoka T, Nishimura M, Kakinuma S, Hatano Y, Ohmachi Y, et al., (2007)
23. Dahl LK, Heine M, Tassinari L (1962) Effects of chronic salt ingestion evidence
22. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, et al., (1994) Cancer
44. Sassi A, Popielarski M, Synoqiec E, Morawiec Z, Wozniak K (2013)
40. Quan X, Laes JF, Stieber D, Riviere M, Russo J, et al., (2006) Genetic
38. Petersen M, Pardali E, van der Horst G, Cheung H, van den Hoogen C, et al.,
35. Grimshaw MJ (2005) Endothelins in breast tumour cell invasion. Cancer Lett
34. Ding SL, Yu JC, Chen ST, Hsu GC, Kuo SJ, et al., (2009) Genetic variants of
33. Broberg K, Huynh E, Schlawicke Engstrom K, Bjork J, Albin M, et al., (2009)
31. Sorensen KD, Abildgaard MO, Haldrup C, Ulhoi BP, Kristensen H, et al.,
27. Cronkite EP, Shellabarger CJ, Bond VP, Lippincott SW (1960) Studies on
25. Shellabarger CJ, Stone JP, Holtzman S (1978) Rat differences in mammary
22. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, et al., (1994) Cancer
46. Lv ZD, Kong B, Li JG, Qu HL, Wang XG, et al., (2013) Transforming growth
45. Smollich M, Gotte M, Yip GW, Yong ES, Kersting C, et al., (2007) On the role
22. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, et al., (1994) Cancer
21. Rouchers CM, Erdmann CA, Land CE (2004) Radiation and breast cancer: a
22. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, et al., (1994) Cancer
48. Deming SL, Zheng W, Xu WH, Cai Q, Ruan Z, et al., (2008) UGT1A1 genetic
47. Ockenga J, Vogel A, Teich N, Kein V, Manns MP, et al., (2005) UDP
46. Zhou Y, Kato H, Shan D, Minami R, Kitazawa S, et al., (1999) Involvement of
45. Smollich M, Gotte M, Yip GW, Yong ES, Kersting C, et al., (2007) On the role
20. Subramanian MM, Chan JY, Soong R, Ito K, Ito Y, et al., (2009) RUNX3
19. Sasaki A, Popielarski M, Synoqiec E, Morawiec Z, Wozniak K (2013) ALA
18. Sasaki A, Popielarski M, Synoqiec E, Morawiec Z, Wozniak K (2013) ALA
17. Sasaki A, Popielarski M, Synoqiec E, Morawiec Z, Wozniak K (2013) ALA
16. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
15. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
14. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
13. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
12. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
11. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
10. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
9. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
8. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
7. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
6. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
5. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
4. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
3. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
2. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3
1. Imamura Y, Hibi K, Koike M, Fujiwara M, Kodera Y, et al., (2005) RUNX3

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